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VIRUS DISEASES: SOME LABORATORY PHASES

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ALTHOUGH Jennerian vaccination[1] was introduced in 1796, long before the causative agent of smallpox was suspected, and the epoch-making discovery by Pasteur, Chamberland, and Roux[2] of the immunization of dogs against rabic infection was reported in 1884, the study of virus diseases and viruses is of comparatively recent date. During the past few years much has been written on the subject, and it is hoped that analysis, interpretation, and evaluation will soon establish the fact that much has been said.

The newer knowledge of viruses and virus diseases has presented many problems to the laboratory study of these agents and maladies. In the first place, we can no longer be content in the use of such terms as filtrable virus or ultramicroscopic virus in application to this particular group of disease agents, for certain forms of bacteria pass through the ordinary filters and certain viruses are now known to be as large as some of these bacteria. Furthermore, the use of ultraviolet and fluorescent microscopy and the new electron microscope bring the smaller viruses within the range of visibility. The conception of a "contagium vivum fluidum" suggested by Beijerinck[3] in 1898 to designate the active principle producing a virus disease as different from bacterial agents cannot now be accepted as determinative. Although there is implied by such a term a filtrable nature, a living and contagious character to such an agent, greater specificity and more exact differential criteria are now required. It has quite definitely been established that viruses are of particulate nature by the demonstration of elementary bodies in a number of virus diseases. A rather accurate measurement of the size of virus particles by means of filtration through collodion membranes of graded porosity and their centrifugation at high speeds

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has shown clearly furthermore the approximate range of the whole series of viruses and that those in each disease are represented by particles of fairly constant size.

Thus, through the gradual accumulation of knowledge concerning these particular agents of infectious diseases, it has been necessary to drop the qualifying terms "filtrable" and "ultramicroscopic," and to use the simple name "virus" as a general designation for the group of pathogenic agents to be distinguished from bacteria and other infectious agents of already established nomenclature.

What, then, is a virus? A precise definition is almost impossible to give if it were to include all of the varieties within the characterized group. Nevertheless, certain peculiar characters so far detected and found to persist in the majority of cases give some justification for the grouping. The most important of these characters are size and filtrability, inability to grow on media without the presence of living cells, persistent parasitism of tissue cells, and the production of characteristic intracellular changes. Although our present interest is that of viruses which attack man, it is of especial interest here to note that animals, plants, and even bacteria are victims of virus disease and that much of the knowledge attained has been through the study of such animal and plant diseases. The growth of the early knowledge began in 1892 when Iwanowsky[4] found that the mosaic disease of tobacco plants could be transmitted by an agent which would pass through the pores of an earthenware filter sufficiently fine to hold back ordinary bacteria. Again in 1898, Loeffler and Frosch[5] demonstrated in the same manner that the virus of foot-and-mouth disease of cattle was a filtrable agent. Three years later Walter Reed and his co-workers[6] established the filtrable nature of the yellow fever virus, and since then a large number of infectious diseases of man have been shown to be caused by similar agents. This characteristic of filtrability is still considered one of the dominant features of virus, notwithstanding the previously mentioned fact that some bacteria will also pass through the filters. In the general biologic divisions there is hardly an example where some overlapping does not take place, and this indefinite border line between bacteria and viruses should not alter the given biologic positions. Filtrability implies a size less than 0.2 μ, which is exceeded by bacteria, with a few exceptions. The measurements of the size of viruses indicate a range from 0.2 μ (200 mμ) to 0.01 μ (10 mμ).

Viruses appear to propagate in the body because serial transmission of virus diseases in animals denotes growth and multiplication of the virus; yet, unlike bacteria, they have never been cultivated on lifeless culture media. This is one of their most significant characteristics, for laboratory cultivation is possible only on the membranes of, or in the embryo of, the developing hen's egg, and in vitro on a culture containing fresh animal or embryonic tissue.

Parasitism is a universal attribute, and it is a restricted parasitism in the true sense, for viruses parasitize only within tissue cells, often only within a certain type of cell. In some cases the specificity for tissue and even for species has remained constant, whereas in others, variations are observed. They can adapt themselves to different tissue environment, as shown for example by propagation of yellow fever virus in the brains of mice, and they can be established in growth in animals they do not normally infect, as in the case of the human influenza virus made to grow in mice. Abnormal intracellular changes and structures result from the parasitism, in the form of inflammatory reaction, degeneration, and necrosis of the cells. In some instances even extensive proliferation of cells is stimulated, thus giving rise to neoplastic lesions. Added features in the occurrence of cellular inclusions have been described in certain virus diseases. These may be observed in the form of bodies varying in size and shape, of indefinite structure, present in the cytoplasm, as in rabies and vaccinia, or within the nucleus, as in yellow fever. Such inclusions were first thought to be products of degeneration, but are now considered to be aggregates of virus bodies or masses of the elementary filtrable forms resulting from multiplication in the cell.

It can now be suggested that the laboratory study of viruses involves some new and added principles in addition to the commonly practiced ones in other infectious diseases, and this study demands specialized equipment and unique and ingenious interest accompanied by an applied philosophy. After all, it was a philosopher, Robert Boyle, in the seventeenth century who prophesied that the problem of infectious diseases would be solved by him who elucidated the nature of fermentation. The prediction was fulfilled later by Schwann, a botanist, Caignard-Fatour, a physicist, and Pasteur, a chemist. Philosophy as investigation of facts and principles of reality is valuable in present-day virus study, and workers in the specialized fields of medical research, e.g., clinical medicine, pathology, bacteriology, and biochemistry, are as essential to the further progress of the study as those men were in establishing proof for the germ theory of disease.

Within the limits of this paper it will be impossible to review all of the most outstanding problems in the virus field, but it is hoped that a few of practical nature may be correlated with other recent advances in the medical sciences.

THE NATURE AND PROPERTIES OF VIRUSES

Aside from the characteristics mentioned earlier, there are other properties, both chemical and physical, which greatly influence interpretations of the "virus problem." The most outstanding problem and fundamental question is their place in nature—whether they are living organisms or inanimate substances. A consideration of the larger viruses

may show that they are similar to bacteria, and study of the smaller viruses reveals a similarity to protein molecules. The elementary bodies found in certain virus diseases are not unlike bacteria in morphologic appearance, for they may appear in pairs, short chains, or irregular coccoidal groups. By filtration and washing, the elementary bodies of vaccinia may be purified, yet still maintain their infectivity. It has been shown by Rivers and Ward that a measurement of the infectivity of such a virus suspension can be made by the number of particles present, and that infectivity is lost when all elementary bodies are removed. A serologic response is also noted when the purified particles are injected into a laboratory animal. The specific antisera produced will neutralize the virus and clump or agglutinate the particles in the same manner as bacteria are agglutinated by their specific antisera. Therefore, it may be held that such a virus represents a microorganism differing from bacteria in its strict parasitic habits, requiring perhaps the enzyme system of the host cell. The virus will multiply in the cell because the already functioning environment supplies the needs which it cannot provide itself in an independent existence. With respect to the smaller viruses such as those of poliomyelitis, foot-and-mouth disease, and certain bacteriophages, which range from 8 to 15 millionths of a millimeter, it is much more difficult to prove their capacity for living. Other than the serologic reactions which have been determined in poliomyelitis and foot-and-mouth disease viruses, very little is known concerning their properties.

In support of the chemical theory of viruses, the work of Stanley[7] (1935) is of outstanding importance. By chemical methods similar to those employed with the crystalline proteins, he obtained a purified crystalline protein from diseased tobacco plants which possessed the properties of tobacco mosaic virus. Further analysis of this crystalline substance showed that it was similar to other proteins in composition, yet it maintained its infectivity. Other workers have repeated this work with the same and other plant viruses, but as yet there is no convincing evidence that animal viruses or those from human diseases are heavy proteins. We are confronted then with different views and theories on the living nature of viruses—that smaller plant viruses are crystalline or nucleoproteins, while the larger ones are parasitic microorganisms. As has been pointed out by Laidlaw and Green independently, this diversity can be reconciled only through studies of the evolutionary origin of viruses.

Other chemical and physical features have been determined as common to some, but not constant for the whole series. Many are resistant to 0.5 per cent phenol and various concentrations of formaldehyde. Vaccinia and rabies virus withstand the action of phenol for fairly long periods of time. In tests with 5 per cent monkey cord suspensions in

0.2 per cent formalin kept at incubator temperature for two days, the presence of active poliomyelitis virus was demonstrated by the typical disease in monkeys. A 1:5,000 dilution of formaldehyde will destroy the activity of influenza virus in less than a week. Fifty per cent glycerol will preserve many viruses, especially in tissue, while bacteria die. Viruses, as well as bacteria, are destroyed by ultraviolet light. The sensitivity to heat is about the same as that of nonsporing bacteria, 50 to 55° C., and most viruses withstand drying. Turner[8] (1938) and Horsfall[9] (1940) have shown that influenza virus suspensions can be repeatedly frozen and thawed over long periods of time without destroying their infectivity, providing the freezing is done rapidly at –70 to –80° C.

CLASSIFICATION OF VIRUSES

It is quite evident that all viruses are not similar and thereby constitute a rather heterogeneous group. There is too little knowledge of their biologic nature to do much more than group them for practical purposes. For clinical and epidemiologic interest virus diseases may be grouped as human or animal diseases, and a division in subgroups according to the tissue attacked has been commonly employed. A definite group may be classified as neurotropic, in which the nervous system is involved; another may be called dermotropic by their association with lesions of the skin; and some have been recognized as viscerotropic or pantropic types of viruses. At times variations in adaptation to different tissues can be found, as witnessed by the virus of vaccinia, primarily dermotropic but acquiring neurotropic affinity when injected into the brain. Likewise, the viscerotropic yellow fever virus develops neurotropism upon passage in mouse brain.

A catalogue of viruses arranged according to size, even though it might be complete, would not be a satisfactory basis for classification. The more or less exact determination of size, however, is of certain advantage to the research worker in the investigation of new strains and elimination studies. The development of "gradacol" membranes by Elford[10] has greatly enhanced the ease and accuracy of these determinations. By a special technique, collodion membranes are prepared in thin sheets with great uniformity of pore size, and by altering the conditions in the preparation, membranes of different pore size can be obtained. When a virus suspension is filtered through a series of these membranes, the probable size of the virus can be calculated by a determination of the pore size of the membrane which just retains the virus. The development, by Bauer and Pickels, of an air-driven ultracentrifuge with an optical system, modified after that devised by Svedberg, enables direct photographic measurements of the sedimentation rate of the virus particles. From this rate it is possible to arrive at the actual size of the virus. A comparison of the size by the two

methods shows close agreement, allowing an assumption that the approximate size of the infectious agent in a number of virus diseases is established.

ISOLATION AND IDENTIFICATION OF VIRUSES

The diagnosis of all infectious diseases by laboratory methods is accomplished through one of two avenues of approach: (1) the recovery and identification of the agent known to be the cause of the particular disease; and (2) serologic testing to determine the presence of specific antibodies which are formed in response to the invasion of the organism. Since it may be concluded, for the moment at least, that virus diseases belong to the large group of infectious diseases, but differ in the nature of the infective agent, the lines of approach are the same as those applied in bacteriology, parasitology, and mycology. It is nevertheless obvious from the evidence already presented that certain diversions and modifications of the usual routine methods are necessary and that the detailed study is still a problem of the research laboratory. Because of inability to observe with ease the virus in microscopic preparations and to employ the usual culture media, the presence of the viral agent in lesions can be determined only by injection of the proper material from the patient into a susceptible animal or fertile egg. Because of the strict parasitism of the virus toward cells of the nervous system in rabies and poliomyelitis, such procedures are possible only at post-mortem examinations as only virus recovered from nervous tissue can be indicative. The long-established histologic method of examination for Negri bodies in the brain from suspected rabies cases is quite reliable, for these inclusion bodies are so characteristic in their morphology. In several other virus diseases, inclusion bodies with characteristic structure such that they are not confused with other structures are associated with the infectivity of the tissue in which they occur; namely, Guarnieri bodies in smallpox, Miyagawa bodies in lymphogranuloma inguinale, Henderson-Paterson bodies in molluscum contagiosum, and those in psittacosis and trachoma, unnamed as yet. But in poliomyelitis only indefinite intranuclear inclusions have ever been seen; thus, the injection of medulla or spinal cord material into a monkey is the only recourse to proof of virus infection, and it is particularly fortunate that this animal exhibits symptomatologic reactions identical with those in human beings. The pathology of the disease in monkeys is also similar to that of the human disease. A discussion of the pathology of virus diseases, however, does not come within the scope of this paper. The passage of poliomyelitis virus from man to monkey is not always an easy or certain accomplishment, as may be exemplified by a summary of the investigations of Stimpert and Kessel[11] during an outbreak in Los Angeles in 1939. Extensive studies of seventeen human autopsy cases

revealed the presence of virus in the cord-medulla preparations in nine instances by serial passage in monkeys. Injections of brain preparations from sixteen of the autopsy cases, of the olfactory bulbs and mesenteric lymph nodes from ten, and the liver and spleen from three, failed to induce the typical disease in animals. In only one attempt to recover virus from tonsils and in another from adenoids were the results positive, the significance of which cannot be interpreted at the present time. Spinal fluid from 100 patients and blood from a large number of patients hospitalized during the outbreak were tested in monkeys, with completely negative results, which gives added evidence that the virus of poliomyelitis restricts itself to the motor cells of the nervous system.

With lymphocytic choriomeningitis, a rarely fatal virus infection, the conditions for recovery of the virus are not so complex. Armstrong and Wooley[12] (1935) and Rivers and Scott[13] (1935, 1936) demonstrated clearly that the virus was present in the cerebrospinal fluid, while other workers have since isolated it from blood, urine, and the nasopharynx. Mice, guinea pigs, and monkeys are susceptible, and any of these animals can be used for isolation of the virus by intracerebral and intraperitoneal injections of blood or spinal fluid collected early in the disease. As this virus may be found in a latent state in apparently healthy mice, care must be taken to assure virus-free stock. Armstrong and Sweet[14] (1939) have recently recovered the virus from wild mice caught in the houses of two persons ill with the disease. Serum-neutralizing tests are of value as an aid in diagnosis, for often the case is not seen in the early stage.

When the isolation of a virus from human beings is attempted, the proper choice of laboratory animal is essential, as the variation in adaptability is sometimes extreme. Although suspected of being a disease of virus etiology, extensive investigation of human epidemic influenza was not possible until it was discovered by Smith, Andrewes, and Laidlaw,[15] in 1933, that ferrets inoculated intranasally with nasal washings from influenza patients became ill with typical features of an influenza attack. After the virus had been established by transmission from ferret to ferret, it was found by these workers and independently by Francis[16] (1934) to infect mice also. Recently it has been claimed that certain strains of the virus may be isolated by inoculating mice directly with throat washings.[17] Perhaps even more remote seems the report of Taylor[18] (1940) of detecting human influenza virus in throat washings by an immunity response in the Syrian hamster.

It does not obtain, therefore, that viruses in general are more likely to be adapted to species more closely related to the one in which the disease occurs spontaneously, although this circumstance has appeared to persist predominantly in the common cold, measles, mumps, and

poliomyelitis, where only the chimpanzee or monkey can be infected. The claim by Armstrong,[19] in 1939, that the Lansing strain of poliomyelitis has been successfully transmitted to cotton rats from monkeys, and subsequently from the rat to mice, is of great momentous interest. The yellow fever virus is pathogenic to mice, guinea pigs, and bats when injected intracerebrally, and yet the hedgehog has been successfully infected intraperitoneally and subcutaneously,[20] giving rise to viscerotropic lesions. The ferret, rabbit, and golden hamster are resistant, and there is no evidence that the virus multiplies at all in these animals.[21]

That a wide variety of animals are necessary for virus investigations is apparent, and it should at once be obvious that when such factors are involved, which, for lack of more certain terms, may come under the title of "the unknown biologic element," the difficulties to overcome in securing unqualified results are great. Many advantages have been found through the use of the fertile hen's egg and tissue culture in the study of viruses which can be propagated by either one of these methods.

CULTIVATION OF VIRUSES

Recent advances have been possible since Goodpasture and his coworkers,[22] in 1931, introduced the use of the developing chick embryo as a method for the propagation of viruses. The fertile hen's egg has been found to furnish particularly suitable conditions for the multiplication of a large number of viruses, notwithstanding the fact that certain of them have shown varied selectivity in species of animals. The favorite tissue for use in virus inoculations is the chorio-allantoic membrane in a ten- to twelve-day egg; the method ingeniously developed by Goodpasture is to cut a window in the shell and shell membrane of the egg, previously treated, exposing the chorio-allantois. The inoculum is then placed on the membrane and a cover glass sealed over the window. By this method, or modifications thereof, the following human viruses have been propagated in serial passage; influenza, common cold, measles, psittacosis, yellow fever, St. Louis encephalitis, Japanese encephalitis, lymphocytic choriomeningitis, lymphogranuloma inguinale, and herpes. Usually the original inoculum for the egg passage is a suspension of infected animal tissue where the virus is present in considerable quantity, but Francis[23] (1937) has isolated the virus of influenza by direct inoculation of the egg with nasopharyngeal washings without preliminary animal passage. Rake and Shaffer[24] have also recently reported the successful isolation of measles virus from throat washings.

Other tissues of the developing embryo are also favorable for the growth of viruses, and direct injection into the embryo or yolk sac has given successful results. Dawson[25] has been able to cultivate the

virus of rabies by direct injection into the brain of developing embryos. Using Cox's[26] yolk sac method for the cultivation of rickettsia, Stimpert[27] (1939) found the viruses of St. Louis encephalitis and lymphocytic choriomeningitis to multiply in the embryo proper.

Tissue cultures in the form of particles of minced tissue from chick or mouse embryos covered with Tyrode's solution in a suitable tube or flask have also been successfully employed for the cultivation of a wide variety of viruses. All of the viruses propagated in the developing hen's egg can also be grown in tissue cultures, and in addition to these, the successful cultivation of the viruses of rabies and poliomyelitis has been described. Webster and Clow[28] (1936) cultured rabies virus in a serum-Tyrode solution with mouse or chick brain. Rat or mouse embryo brain in chick plasma was also used with success by Bernkopf and Kligler[29] (1938), and such virus has been used in the experimental vaccination of dogs. By using a Tyrode solution containing minced nervous tissue of 4-month-old human embryo obtained by cesarean section, Sabin and Olitsky[30] (1936) were able to obtain growth of poliomyelitis virus. Typical infection was produced in monkeys by the sixth subculture in a dose representing a dilution of 1:1,000,000 of the original inoculum. The practical significance of the cultivation of viruses by these methods may well be anticipated, for already application has been made to the study of inclusion bodies and properties of viruses, titration of antiviral sera, direct isolation of virus and the preparation of vaccines for human immunization. Some of these studies are already in progress.

SEROLOGY AND IMMUNOLOGIC REACTIONS

The fact that one attack of smallpox, measles, mumps, poliomyelitis, and yellow fever usually produces a long-lasting immunity is appreciated. The presence of antibodies in the blood of the recovered person has been widely demonstrated, but the relation of these antibodies to the actual immunity is not clearly understood. Without going into the discussion of immunity to virus diseases in human beings and animals, I would like to conclude with a few examples which show the application of immunologic reactions.

The immunologic principles applied in the study of bacteria hold for viruses, and the serologic phenomena of precipitation, agglutination, and complement fixation, along with neutralization tests, which are most widely employed in virus studies, are applicable. The greatest difficulty with the first three is that, for a reliable test, the virus antigens should be in a comparatively pure state. In order to attain this, they must be separated from tissue containing them. With the neutralization tests this is not always necessary and centrifugalized or coarsely filtered virus suspensions may be used. A mixture of the de-

sired dilution of serum to be tested and the virus suspension are incubated, and the resulting mixture is injected into susceptible animals to determine whether the serum contains the specific antibodies. If the animals remain normal, it is assumed that the serum has neutralized the virus.

Extensive use of the virus neutralization tests has been made in epidemiologic studies and for the identification and comparison of virus strains. It is generally agreed that about 75 per cent of the sera from normal adults neutralize the virus of poliomyelitis, and over 70 per cent neutralize the virus of influenza. These findings lead one to assume that such persons had, sometime earlier, inapparent infections and that probably mild strains of virus are widespread. Similar neutralization studies have been carried out with other viruses and are significant in the interpretation of such tests used for diagnostic purposes. Magill and Francis[31] (1938) were able to show varying differences among twenty-four strains of influenza virus, and just recently Francis[32] (1940) reported a strain which is not at all similar in immunologic reactions to any of the others. Differences have also been found to exist among a number of strains of poliomyelitis virus, as reported by several workers.[33-35] The significance of strain differences, though not sufficient for a basis of classification, certainly suggests the necessity of consideration in epidemiologic problems and in the possible future prophylactic and therapeutic studies.

The complement fixation test has proved a great aid, not only in experimental work but in the diagnosis of certain virus diseases as well. The performance of these tests, however, is limited to a few research laboratories. In yellow fever, lymphocytic choriomeningitis, psittacosis, and influenza, complement-fixing antibodies are present in sera of patients, and antigens prepared from virus-infected tissue of animals have so far been found to be specific and reliable. A rigid control system should be included with each test, nevertheless, to eliminate any possible false reactions.

It must be remembered that single serologic tests are of little value in the diagnosis of many virus diseases because of the possibly wide existence of antibodies in sera of the normal population. Blood must be tested, therefore, early in the disease and again several weeks after convalescence to determine whether there is a significant rise in antibody titer.

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THE PATHOLOGY OF VIRUS DISEASE

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VIRUSES are known by what they do, that is to say, in very large measure by the lesions they induce. Under some circumstances, it is true that infection by them may result in a general manifestation such as a mild febrile illness unassociated with obvious cellular abnormality, or an inapparent infection might be followed by the specific phenomenon of serologic antibodies, but the fundamental basis of knowledge of virus activity in the infected host lies in the cellular changes observable in the lesions the viruses cause. From this assertion, which I think will hardly be gainsaid, it is self-evident that the techniques and discipline of anatomic pathology are indispensable to the obtaining of a broad conception of virus diseases.

The pathoanatomist became familiar in the past with the response of hosts to a variety of the commoner pathogenic microorganisms. Acquisition of this knowledge was greatly facilitated by the ability to cultivate microorganisms in pure strain and to demonstrate them by staining methods in association with lesions. Although many protozoa cannot be cultivated, their morphologic characteristics sufficed for their recognition and identification.

Much attention has been paid in the study of lesions of infective diseases to their general histologic features, such as the suppurative processes and granulomas exemplified by the abscess and the tubercle. Cellular detail has not dominated interest in the past partly because of insufficient knowledge of normal cytologic structure and deviations therefrom to afford a background for interpretation of specific alterations.

The general run of infectious lesions that the pathologist sees are caused by microorganisms, usually bacteria, that grow and disseminate within the fluids of the body. The ordinary technical procedures for demonstrating them morphologically in relation to lesions are such as to obscure considerably the cellular detail, and they require special methods and extra time for their preparation. The histopathologist, as a rule, views an infectious lesion as a tissue response, that is, an inflammatory reaction, so that his chief interest is in the general composition of the abnormal cellular aggregates. If bacteria are discovered within cells, his readiest interpretation is that phagocytosis is a combative response.

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In the study of virus lesions, however, the emphasis is different, for interest is focused immediately upon the alterations of the cells themselves rather than their aggregate effect. Viruses affect cells, often only a restricted type of cell, and in ways highly original and characteristic. The student of virus diseases, therefore, must have an understanding of cytology if he is to be enabled to interpret the cellular phenomena intelligently. Whereas the lesions caused by the commoner bacteria may be primarily of interest in their histologic aspects, those caused by viruses are problems specifically of the participant cells.

Striking ways in which viruses can affect cells may be illustrated by the lesions of some of the virus infections of man. Predominant in certain instances is cellular hyperplasia, to be observed especially well in warts. Verruca vulgaris occurs commonly on the skin of the extremities and the same virus less frequently causes infectious papillomas of the larynx. The essential feature of the nodule is hyperplasia of epithelial cells. There may be little or no inflammatory exudate, and little or no cellular degeneration other than excessive keratinization and desquamation. The wart viruses which constitute a group of pathogenically and antigenically distinct entities characteristic for certain species of animals are highly specific for squamous epithelium. One of them at least, namely, that of oral papillomatosis of dogs, is further restricted in its effects to squamous epithelium of the mouth; that of the lips, skin, conjunctiva, and genitals, for example, remains unaffected by it following inoculation.[1]

Another virus infection of man, molluscum contagiosum, likewise affects the cutaneous epithelium, and seems to be restricted entirely to these cells. The umbilicated nodular lesions are essentially the result of epithelial hyperplasia, as are those of warts, but in addition to stimulating excessive growth of epithelium, this virus causes very marked and specific structural changes in the affected cells that are of profound significance. These changes are of the nature of cytoplasmic inclusions, composed for the most part of thousands of minute, uniform, coccoid granules that are just visible with high magnification, but can be readily stained by suitable methods.[2] These are the so-called Lipschutz granules or elementary bodies, which from analogy with certain other virus infections, notably fowl pox, smallpox and vaccinia, may be assumed to represent the virus particles themselves. Similar elementary bodies occur in the lesions of the diseases last mentioned, and they enter into the composition of the respective cytoplasmic inclusions. In these lesions also there is some degree of epithelial hyperplasia most marked in fowl pox.

There are other virus diseases in the specific lesions of which cellular disintegration is the dominant feature; and this may occur without hyperplasia or the formation of inclusions, as in mumps and poliomyelitis. In the former, as indicated by experiments with

monkeys, the epithelial cells of the parotid gland undergo necrosis to initiate the chain of inflammatory events,[3] and in infantile paralysis necrosis of motor cells of the spinal cord occurs most conspicuously.

In herpes simplex, herpes zoster, and varicella, the cellular picture is different in that inclusions appear in the nuclei of affected cells, although, as in smallpox and vaccinia, cellular hyperplasia and lysis are concomitant changes. Somewhat similar changes take place within nuclei, particularly of the epithelial cells of the trachea, bronchi, and alveoli, in the lungs of infants dying of a peculiar pneumonia which we recently described and attributed to an as yet unknown virus.[4] In the lungs of children and in cells of other organs as well, notably the kidney, a virus not yet adequately studied causes another and quite distinctive cellular change characterized by a great increase in size. The cells contain within their nuclei large acidophilic inclusions, and sometimes basophilic bodies occur which might be specific inclusions within the cytoplasm. This is the so-called "inclusion" disease or "visceral" disease. Similar infections appear in some lower animals, such as the guinea pig and the mouse. Experiments with these animal diseases have conclusively shown that the cellular changes described are due to infection by viruses.

In a general way the course of events in the human diseases that I have mentioned seems fairly clear. Warts and the eruption of molluscum contagiosum arise as a result of direct infection of the skin, and vaccinia is caused by local inoculation; smallpox and varicella in all probability are initiated by a lesion somewhere in the nasopharynx or respiratory tract, followed by a secondary dissemination of virus through the blood stream, which localizes in the skin, with the resulting eruption of pocks.

Now we will consider another group of virus diseases that seem relatively obscure in their pathogenesis, that is, the group which affects especially the central nervous system, represented in man by such examples as rabies, poliomyelitis, and equine encephalomyelitis.

In the case of rabies and poliomyelitis the virus is not to be found in the blood, and the portal of entry of the former is usually the site of the bite of a rabid dog. After a variable interval it reaches the central nervous system, to bring about destruction of nerve cells and to cause the deposit in neuronal cytoplasm of characteristic structures known as Negri bodies which are the specific cellular inclusions of this disease. The virus affects especially profoundly sensory ganglion cells, although motor cells do not escape. It is rather the reverse with the virus of infantile paralysis which destroys predominantly motor cells, especially those of the anterior horns of the spinal cord.

Although it too affects the central nervous system predominantly, the virus of equine encephalomyelitis presents other manifestations that differ from those of rabies and poliomyelitis. In the first place,

it appears in the blood stream and seems to attack interstitial tissues of the brain as well as neurones.

Other significant illustrations of the effects of virus infection could be cited, but these are surely enough to emphasize the striking individuality these pathogenic agents manifest, and to excite an interest in the manner of their behavior in reference to cells of the host and in the pathogenesis of the diseases they induce. The question naturally arises as to whether or not the various patterns of infection with their specific cellular effects and other phenomena can be harmonized by some general concept of virus activity.

Certainly most investigators of viruses and their effects would at the present time answer this question in the affirmative, regardless of their point of view as to the nature of these agents, because the theory of cytotropism or intracellular parasitism of viruses is now quite generally held, and it serves a useful purpose both as an aid to an understanding of the diverse patterns of pathogenesis and as a stimulus to research.

There is really no acceptable evidence that any virus will multiply in an acellular medium either in vivo or in vitro. On the other hand, a large number of viruses have been cultivated outside the body in the presence of living cells. It is impressive too that the cellular changes which viruses induce are highly characteristic and probably always specific, and they are associated with the multiplication of viruses.

There is also considerable positive morphologic and experimental evidence that certain viruses require living cells for their multiplication and that increase in a virus takes place within the viable intracellular medium. As illustrative of this type of evidence, I would like to call your attention first to studies of an eruptive disease of birds, namely fowl pox. Dr. C. E. Woodruff and I demonstrated several years ago that a weakly alkaline solution of trypsin would free the specific cellular inclusions of fowl pox from infected epithelial cells, so that they could be washed free of virus in the suspending medium and manipulated as units. We showed that a single washed inclusion inoculated into a feather follicle caused fowl pox infection at that site.[5] Even a fraction of an inclusion would act similarly, and because each inclusion is composed of several thousand elementary bodies, this evidence indicated very directly that these granules are associated with the virus of this disease; and together with other evidence of an immunologic nature, it is a fair conclusion that they are the viral units. We have likewise demonstrated that the elementary bodies of vaccinia and of molluscum contagiosum are intracellular and constitute the most important component of the respective cellular inclusions.

There is morphologic evidence also from the study of other and unrelated viruses, for example, that of psittacosis, that propagation within susceptible living cells occurs, and it is quite reasonable to explain the lesions and the pathogenesis of the diseases they cause on this basis. But what of those that manifest themselves by an attack on the central nervous system, especially in instances such as rabies and infantile paralysis, in which it is difficult or impossible to demonstrate virus in the circulating blood and in which abundant evidence indicates invasion by way of nerves?

Following the bite of a rabid animal, there is no proved local infection by the virus, but after a variable length of time central nervous symptoms appear, and as was demonstrated by Pasteur, the virus is present in the brain and spinal cord. Without the demonstration of virus in the circulating blood, one cannot explain the pathogenesis of rabies by an assumption of metastatic infection by that route, nor is such an assumption needed in view of the direct evidence that peripheral nerves can serve as pathways for the virus to proceed from a peripheral site of inoculation to the brain or cord. So the question to be determined is the course the virus pursues in its progress along the nerves.

This question was much in the foreground in early experimental studies of infection in rabbits with the virus of herpes simplex. Doerr and Vochting showed that rabbits whose corneas had been infected with the fever blister virus frequently died of herpetic encephalitis, and they assumed, although without adequate experimental evidence, that the virus localized in the brain from the blood stream. Levaditi was unable to accept this explanation and invoked a more direct approach through the fluid about the optic nerve, a view difficult to understand even on anatomic grounds. A sounder interpretation was indicated by the observation of Friedenwald that active virus could be demonstrated in the gasserian ganglion homolateral with the infected cornea of a rabbit, and this led him to suspect that the virus enters the central nervous system through the direct pathway of fibers of the sensory division of the fifth cranial nerve which innervate the cornea.

This course of invasion was thoroughly proved by Teague and the author and by Marinesco and Draganesco, but the latter authors maintained that the virus proceeded from the periphery to the central termination through perineural lymphatics. Our experiments had indicated that the virus increases *within* the cells which it injures and not within the body fluid, and our interpretation was that the virus reached the central nervous system by multiplication within the axis-cylinders, which form a direct connection between the infected peripheral cells and the bodies of the nerve cells themselves.

This hypothesis was submitted to experimental test by inoculating the masseter muscle of rabbits on one side and studying the changes in the corresponding motor nerve and the fifth motor nucleus as soon as an encephalitis manifested itself. In suitable experiments herpetic changes were observed within the motor ganglion cells deep in the pons before lesions could be found within the nerve or elsewhere. It was concluded from this that the virus passes directly along the axis-cylinders, not by a passive transportation, but by active proliferation in the intracellular medium represented by the extended filament of the nerve cell which extends from the motor nucleus to the periphery, insulated by the myelin sheath.[6] This conception has received further support from the studies of Fairbrother and Hurst with poliomyelitis in monkeys.[7]

Types of encephalitis in which virus has been found to circulate abundantly in the blood stream, at least early in the disease, may have quite a different pattern of pathogenesis that possibly simulates that in cerebral distemper of dogs. The investigation of DeMonbreun with canine distemper disclosed that endothelial cells, and especially endothelial cells of cerebral blood vessels, are quite susceptible to infection, and it seems likely that the cerebral manifestations of the acute form of the disease are due to this fact. It is probable also that the later-appearing distemper encephalitis is brought about, not by peripheral neural infection, but by virus entering through infected endothelial cells and coming thereby in contact with neurones, to invade them directly.[8] This may be the mechanism of infection in encephalitis caused by the equine virus.

Thus, from many points of view the conception of cytotropism has received continued support, and its acceptance as an experimental hypothesis affords a reasonable basis for projecting further research into the mechanism of virus infections. The idea of intracellular growth of infectious agents is not a novel one, for protozoologists have long been aware of obligate cellular parasitism by many of these unicellular organisms, and it is now well known that the bacteria-like rickettsia have a similar relation to the cells they infect. Although the idea of intracellular parasitism of bacteria has not received much emphasis, there is recent support of the point of view that obligate and facultative cellular bacterial infections also play significant roles in many host-parasite relationships. It would seem obvious that, if some infectious agents like the viruses and rickettsia, many protozoa, and certain bacteria require an intracellular environment, and that others can utilize that medium for growth and invasion, this fact would have important implications relative to pathogenesis of infective diseases, to the processes of resistance and immunity, and to sero- and chemotherapeutic procedures.[9]

While it would be of interest to elaborate this subject further, it would not be practicable on this particular occasion. I should like to emphasize, however, that there is a large and almost unexplored field for the pathologist in the study of mechanisms of infection and invasion of hosts in the very earliest stages of the host-parasite relationship and especially with reference to the participation of susceptible cells as media for parasitic growth and transport. The more we learn about these processes, the closer the tie will appear, I believe, between infections due to viruses and those caused by better known parasites. Cultivation of this field, I may add, is largely a responsibility and opportunity for the pathologist who utilizes the techniques of the morphologist.

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THE BLOOD VOLUME IN NORMAL INFANTS AND CHILDREN

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KNOWLEDGE of the blood volume of normal infants and children is an important part of the therapeutic background in the treatment of the anemias, nutritional and fluid disturbances, and renal and vascular disease. The literature contains four reports on the blood volume of normal infants and children.[1-4] The first three of these authors employed some modification of the original Keith-Rowntree dye method of determining the plasma volume,[5] and the fourth used the CO inhalation method. The reports vary widely as to average normal values and the degree of individual variation therefrom; this makes it difficult to predict normal volume in a given case. No particularly clear relationship as to the correlation between blood volume, age, sex, or physical measurements can be deduced from these studies. None of these authors employed any standards of normal relationship between age and body size. In one report[3] several children had hematocrit values indicative of moderate anemia.

Numerous studies have thrown doubt on the reliability of the older dye methods of determining the plasma volume,[6-9] and it is apparent that the discrepancies in results of previous studies are due to the inaccuracy of those techniques. Because of a previous study of the blood volume in normal adults[10] using a method that has proved to be accurate for clinical use,[8] which has in great measure cleared up the confusion that prevailed in that field, it was thought advisable to extend this study to infants and children.

METHODS

Plasma volume was determined by a method previously described[8] as modified for the photoelectric microcolorimeter.[11] A single determination only was made in each case. Certain modifications were made. In infants the amount of dye given was 1.0 c.c. of a 0.1 per cent solution, or 1 mg.; in the smaller children, 2 c.c. of a 0.25 per cent solution, or 5 mg.; and in the larger children, the usual adult dose of 10 c.c. of a 0.1 per cent solution or 10 mg. of dye. The total amount of blood withdrawn from the infants was from 15 to 20 c.c., from the small children about 20 to 25 c.c., and from the larger children 25 to 40 c.c. In all cases plasma volume was based on the extrapolated value of a disappearance slope derived from not less than four blood samples taken at intervals over a period of not less than thirty minutes after dye injection. When individual samples were insufficient to yield enough serum to fill the colorimeter cup to the standard depth of 10 mm., colorimetry was done with the Koenig-Martens spectrophotometer, using absorption cells of 5 mm. depth. External

From the Departments of Pediatrics, Medicine, and Obstetrics of the Harvard Medical School, the Infants' and Children's Hospital, and the Peter Bent Brigham Hospital.

TABLE I

PLASMA, RED CELL, AND TOTAL BLOOD VOLUME IN NINE NORMAL INFANTS AND FORTY-ONE NORMAL CHILDREN, ALL OF WHOSE PHYSICAL MEASUREMENTS WERE WITHIN ANTHROPOMETRIC NORMS

CASE NO.	SEX	AGE		HEIGHT (CM.)	WEIGHT (KG.)	SURFACE AREA (SQ.M.)	PLASMA VOLUME (C.C.)	RED CELL VOLUME (C.C.)	TOTAL BLOOD VOLUME (C.C.)	HEMATOCRIT (%)	ANTHROPOMETRIC INDICES BY				PERCENTAGE DEVIATION FROM AVERAGE							
		YEARS	MONTHS								HEIGHT		WEIGHT		HEIGHT		WEIGHT		SURFACE AREA		AGE	
											+	-	+	-	+	-	+	-	+	-	+	-
1	M		19 days	49.7	2.96	0.204	164	120	284	42.3		1		2	13.6		29.1		34.0		2.0	
2	F		21 days	52.1	2.99	0.197	130	138	268	51.5		1		2	7.2		21.8		13.6			4.4
3	F		7 days	52.5	3.24	0.207	144	111	255	43.7	1			1	1.0		6.3		2.0		2.0	
4	M		20 days	55.5	3.84	0.233	185	124	309	40.0	3		1		10.2		10.4			3.5	6.0	
5	M		5	64.6	7.14	0.318	300	170	470	36.1	1		1		34.3		4.5		5.7		19.0	
6	M		10	70.0	8.09	0.380	230	146	376	38.9	2			2		9.0		26.3		27.7		24.5
7	M		5	71.0	7.27	0.365	270	156	425	36.7	3		1			1.2		5.6	6.3		18.1	
8	F	1	8	78.0	10.40	0.460	465	300	765	39.1		2		2		19.4	19.6		19.2		17.8	
9	F	1	7	89.0	11.40	0.520	531	305	836	36.4	3		1		13.0		23.0		13.0		26.8	
10	F	2	10	93.4	13.60	0.580	483	347	830	41.8		1		1		1.2		1.2	2.0			6.8
11	F	3	4	95.8	14.55	0.615	653	437	1090	40.3		1	1		22.5		21.1		17.2			11.0
12	M	3	1	99.0	15.45	0.680	593	472	1065	44.4	2		1		9.8		10.9		0.5		13.4	
13	F	3	4	100.2	16.80	0.720	573	457	1030	44.4	2		2		3.0		0			8.9	4.9	
14	F	4	2	100.2	17.1	0.690	568	347	915	38.0		1	1			8.5		12.9		20.7		14.7
15	F	4	1	101.5	17.7	0.690	740	480	1220	39.5		1	1		18.4		13.0			4.9	14.1	
16	F	4	2	104.0	14.5	0.660	585	366	951	38.6	1			3		12.0	8.0			5.9		12.8
17	M	4	11	113.0	19.1	0.810	891	644	1535	42.0	2		1		18.1		32.3		16.3		9.7	
18	M	6	4	114.0	19.0	0.800	815	495	1310	37.8		2		3	0		13.9		·0.8			4.4
19	M	5	10	118.2	21.8	0.870	965	595	1560	38.5	2		2		9.0		15.6		6.9		18.2	
20	M	7	1	119.3	22.7	0.900	934	641	1575	40.7		2		1	7.1		12.5		3.6		7.9	
21	F	7	7	123.4	24.0	0.915	1005	655	1660	39.4		1		1	5.1		10.7		6.4		10.0	
22	F	8	6	125.8	28.4	0.988	885	605	1490	40.8		2	1			10.2		17.2		13.9		9.4
23	F	7	7	127.0	27.7	0.977	1015	565	1580	36.0	1		2			7.1		10.2		7.1	4.6	
24	M	7	11	132.0	24.6	0.990	1000	650	1650	39.3	2			2		12.2	7.1			4.6	6.5	
25	F	9	6	132.6	27.4	1.02	1185	740	1925	38.4		1		1	1.3		10.3		6.9		5.2	

26	M	11	2	133.8	34.4	1.12	1340	900	2240	40.2		3		1	15.5		3.7		6.7		0.9	
27	M	10		135.5	27.8	1.03	1380	780	2160	36.4		1		2	7.5		21.7		16.8		11.3	
28	M	10		135.8	31.3	1.08	1360	940	2300	40.9		1		1	13.3		15.0		16.2		19.1	
29	F	10		139.0	27.8	1.05	1120	990	2010	44.1	1			2		5.5	12.9		6.4		3.1	
30	M	9	10	139.8	27.25	1.05	1170	695	1865	37.3	1			2		14.8	9.6			17.1		0.8
31	M	10	1	141.5	29.3	1.08	1270	790	2060	38.5	1			2		8.9	12.0		4.1		6.8	
32	M	9	5	142.5	29.1	1.09	1340	980	2320	42.3	2			1	1.3		25.4		16.0		28.2	
33	F	9	10	144.0	36.1	1.22	1190	950	2140	44.3	2		2			11.8		7.0		11.2	7.4	
34	F	12	6	147.0	42.5	1.31	1660	1110	2770	40.0		2		1	10.8		0		1.8		9.1	
35	F	14	3	150.0	42.8	1.33	1590	960	2550	37.7		3		2	1.2			7.3		8.9		15.0
36	F	14		153.0	39.0	1.30	1750	1210	2960	40.9		3		3	11.7		18.4		9.7			0.7
37	F	12		153.7	33.6	1.23	1350	780	2130	36.6	1			2		27.3	0			13.0		10.5
38	F	12		155.6	35.8	1.27	1530	970	2500	38.8	1			2		16.7	9.2			2.0	5.0	
39	F	14	9	156.0	57.5	1.55	2335	1490	3825	39.0		2	1		24.2			4.4	6.6		2.8	
40	F	14	8	157.0	49.7	1.47	2030	1290	3320	38.8		1		1	4.7		6.1		0		5.0	
41	F	17		158.0	55.5	1.55	2135	1365	3500	39.0		2		1	7.7			7.9		5.4		3.3
42	M	13	4	159.3	50.0	1.49	2030	1630	3660	44.5	1		1		10.2		10.2		6.4		21.3	
43	F	13	6	160.0	47.7	1.45	2480	1500	3980	37.9	1		1				24.3		17.0		22.4	
44	F	16	6	162.0	53.3	1.55	1850	1490	3340	44.5		1		1		6.7		1.2		9.8		8.4
45	M	15	0	162.5	63.6	1.67	2130	1750	3880	45.1		1	2		7.5			15.6		10.0	1.8	
46	M	16		166.5	58.4	1.64	2520	1840	4360	42.3		1		1	8.2		6.9		4.7			3.1
47	M	15	11	167.0	56.8	1.62	2240	1760	4000	70.6		1		1		2.0	1.0			1.0	5.0	
48	M	15	4	167.4	50.2	1.55	2610	1660	4270	85.2		1		2	4.2		27.8		15.4		4.9	
49	F	15		168.6	49.8	1.55	2335	1445	3780	75.8	2			2		10.0	14.2		2.2		16.3	
50	M	16	1	177.3	65.6	1.79	3250	2580	5830	89.0	2		2		12.2		19.5		13.8		22.2	
Six Children With Physical Measurements Outside Anthropometric Norms																						
51	M		6	64.5	5.2	2.95	227	146	373	39.1		2		4	6.6		9.7		9.1			9.4
52	F	10	6	116.3	20.9	8.50	915	665	1580	42.0		4		4	13.7		22.5		12.1			23.0
53	F	11	4	141.4	25.0	1.02	1130	890	2020	44.2		2		4		10.6		30.3		12.6		10.2
54	M	9	11	147.0	49.1	1.38	1430	1070	2500	42.9	3		4					23.1		16.1	31.5	
55	F	13	8	163.0	70.3	1.74	2330	1420	3750	39.5	2		4		2.7			31.2		22.7	35.1	
56	M	14	11	187.7	71.1	1.94	3340	2610	5950	40.9	4		3			11.2	6.8			11.1	55.7	

jugular veins were used for sampling in infants, and antecubital veins were used in the other children. Novocain injection of the skin at the point of venipuncture was done in all cases, and, once the needle was in position, the infants were quiet throughout the procedure. All samples were taken without stasis. The hematocrit technique used has been previously described.[8] Only one hematocrit was obtained in infants but two to three in the other children, total blood volume being based on the averaged value. No untoward effects were observed as a result of these procedures.

Surface area was determined from the nomograms of Benedict and Talbot[12] in infants and small children and from that of Boothby and Sandiford for the larger children.

Height was taken in children up to 6 years of age as the recumbent length from soles to vertex, measured with a steel tape with the subject lying on a flat surface, and in children over 6 as the standing height.

Fifty infants and children were observed, all of whom were regarded as having normal cardiovascular, renal, respiratory, and digestive systems, and in a good state of hydration and nutrition. The children from the House of the Good Samaritan were convalescent from rheumatic fever, without evidence of heart disease, and with normal temperatures and sedimentation rates. The normal range of hematocrit was taken as from 36 to 44 per cent, except in one newborn infant with an hematocrit of 51 per cent.

There were twenty-four males and twenty-six females in the series. Of the nine infants studied, five were males and four females. There were twenty-six children between the ages of 2 and 12 years, twelve of whom were males and fourteen females. Of the older children, six males and ten females could be said to have arrived at the age of puberty.

The fifty patients observed were within the limits of the normal relationship of age, height, and weight.[13, 14] Three males and three females whose height or weight or both were outside the normal range for age were also studied for comparative purposes.

RESULTS

The data obtained are given in Table I. Absolute plasma, red cell, and total blood volumes are shown by age and sex in Fig. 1. The normal full-term infant has a total blood volume of about 250 c.c. to 300 c.c., and this is doubled during the first year of life. Thereafter, there is a gradual increase until the age of puberty at which time a level of about 2,500 c.c. has been attained. Up to this age there is no difference between the average total blood volume of boys and girls of equal age, but at about the age of puberty the average for boys definitely becomes larger than that for girls. The average total blood volume of children of both sexes who have nearly attained maximum growth is approximately equal to the average volume of normal adult males and females of equal physical measurements.

Inasmuch as the average hematocrit of both groups is about the same throughout the period studied, 40 per cent for both sexes, the increase in

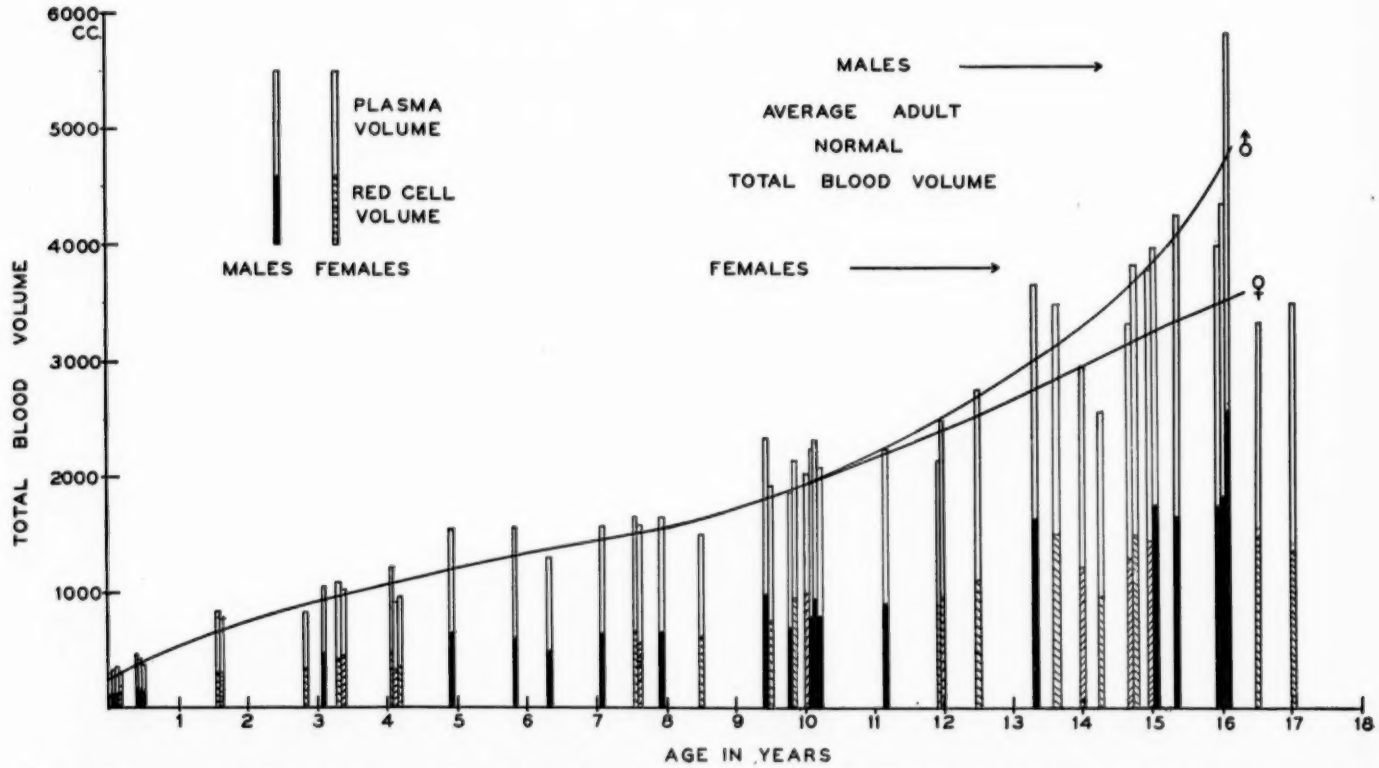

Fig. 1.—The plasma, red cell, and total blood volume in normal infants and children. The solid lines represent the averages for total blood volume for the entire group.

volume with age up to puberty and the more rapid increase in the volume of boys than girls thereafter, is shared proportionately by the plasma and red cell components. The range of individual variations from average values in total blood volume is about the same in both sexes of the series.

The total blood volume bears a definite relationship to height, weight, and surface area in both sexes. There is a progressive rise with increase in all three measurements, which, in the early age brackets, is about the same for boys and girls. In the upper age brackets, when these children can be considered mature or approaching maximum height, if not the estimated maximum weight of later adult life, total blood volume is well within the normal adult range for both sexes and, as in the case of correlation of volume with age, the males have a distinctly higher volume than the girls. This difference becomes definite in the group between 140 to 160 cm. in height, and 40 to 60 kg. in weight, measurements which are within the normal range for the 12- to 14-year age period, or about the time of the advent of sexual maturity.

TABLE II

PERCENTAGE DEVIATION OF INDIVIDUALS FROM AVERAGE VALUES BY CORRELATION FACTORS

CORRELATION FACTOR	DEVIATION FROM AVERAGE TOTAL BLOOD VOLUME					
	±10 PER CENT		±15 PER CENT		±20 PER CENT	
	NO. OF CASES	PER-CENTAGE	NO. OF CASES	PER-CENTAGE	NO. OF CASES	PER-CENTAGE
Age	31	62	39	78	45	90
Height	27	54	40	80	44	88
Weight	22	44	38	76	41	82
Surface area	32	64	38	76	46	92

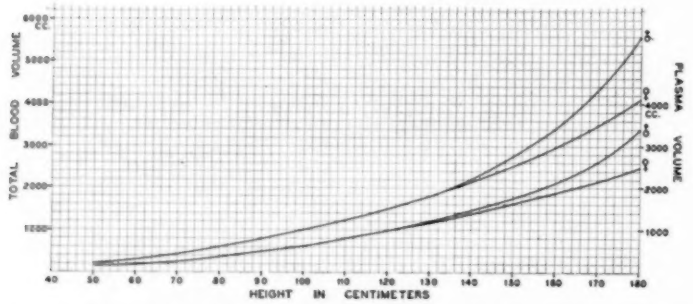

Fig. 2.—Nomogram for the prediction of normal plasma and total blood volume in infants and children. The lower lines represent plasma and the upper lines total blood volume.

Individual deviations from average total blood volume based on the average values by age, height, weight, and surface area are shown in Table II. Although the correlation to all of the factors appears to be

about the same, for reasons discussed below we regard height as the correlative factor of choice for the prediction of normal plasma and total blood volume. Fig. 2 is a nomogram for this purpose.

DISCUSSION

Comparison of our results with those reported in the literature presents some interesting points. We found total blood volume of infants up to 6 weeks of age to be not over 300 c.c. The average value found by the dye method for infants of similar age group by Lucas and Dearing[1] was 460 c.c., by Bakwin and Rivkin[2] 570 c.c., and by Darrow, Soule, and Buckman[3] about 1,000 c.c. The latter authors also studied children up to 12 years of age. Their average value for this age, about 2,000 c.c., corresponds well with our findings, but in the younger age groups average values of all three authors are definitely higher than ours. Total blood volume was found by one author[3] to be almost as great at the age of 2 as at 10 or 12. When compared to our average values based on height, weight, and surface area, total blood volume in every case reported by all three authors is in excess of our values. It is evident that little reliance can be placed upon these results and that therefore they should not be used as a therapeutic guide.

Further evidence as to probability that the figures obtained by the above writers are too high is afforded by the values reported by McIntosh.[4] He determined the blood volume by the CO method in eighteen normal infants ranging from 3.5 to 5.8 kg. in body weight, and his values fall very closely on our average line. In eight instances simultaneous determinations were made by both the dye and CO methods. In six cases the results with the former were much higher than those obtained by the latter method.

A comparison of the reliability of the CO method and the dye method we have employed may be of some interest. We have considerable confidence in the plasma volume as determined and believe it accurately measures the plasma to within about 5 per cent. The question arises as to whether the red cell volume can be calculated with a sufficient degree of accuracy for practical purposes from the plasma volume and an hematocrit determined on blood taken from a large peripheral vein. Smith, Arnold, and Whipple[15] point out that the concentration of cells flowing through the larger vessels is greater than through capillaries and that, therefore, the red cell volume as we have calculated it is falsely high. Recent experiments by Ebert, Stead, and Gibson[16] in which the blood volume was determined by the method we used, in normal subjects undergoing phlebotomy, demonstrated that, as the hematocrit fell following removal of blood and the resultant compensatory blood dilution, the actual red cell volume determined at the anemic level was always lower than the red cell volume

predicted for that level on the basis of the basal volume and the known amount of red cells removed by bleeding. These results show that the discrepancy between true and measured red cell volume at a normal blood level may be somewhat more than the 5 or 10 per cent previously assumed, these figures being based on the differences in the hematocrit of blood samples taken from arteries and veins in various parts of the body. However, since in the technique used hematocrits are always obtained from the blood from the large veins, and since the difference in corpuscular concentration in capillaries and larger vessels is presumably a constant, the determination of total blood and red cell volumes is valid for comparative purposes.

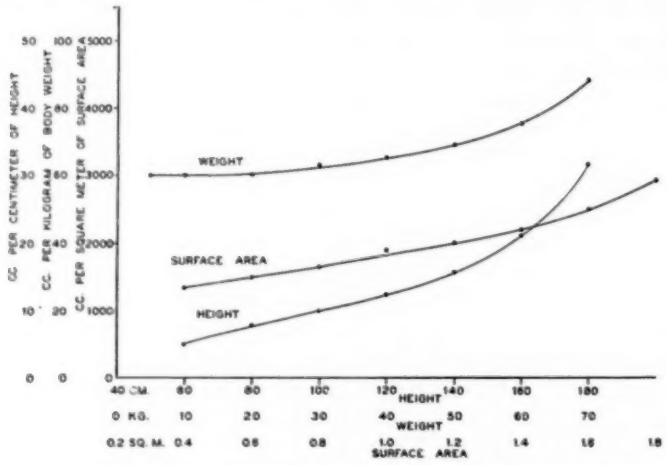

Fig. 3.—The change in unit blood volume accompanying bodily growth.

In the past students of blood volume were looking for an average value of plasma or red cell volume that could be applied as a constant to either age or some physical measurement. Our results show this conception to be erroneous. It is obvious from the data presented in Figs. 1 and 2 that not only do absolute plasma, red cell, and total blood volume increase with bodily growth, but unit volume expressed in cubic centimeters per centimeter, kilogram or square meter of surface area also increases with age. This simple relationship is shown in Fig. 3. It is also evident that this increase does not take place at a constant rate but is accelerated with increase in the physical measurements. Thus, a single formula for normal volume in children of any age could be derived but is too complex for practical use and hence the nomogram (Fig. 2) is preferable.

Plasma and total blood volume are more closely related to physical size than to age. It is of interest to note that just as in our curves total blood volume of boys becomes greater than that of girls of equiva-

lent physical measurements at the age of puberty, so does the normal mean of height and weight to age of boys begin to exceed that of girls at this period. We have classified each child on the basis of his conformity to accepted norms of height and weight to age previously cited.[12, 13] These studies of a large group of infants and children present curves showing the mean value of height or weight at a given age, and curves showing the upper and lower limits of the fractions of the group falling within plus or minus 25, 15, and 10 per cent of the mean value. Assuming a numerical value of zero as corresponding to the mean, we have

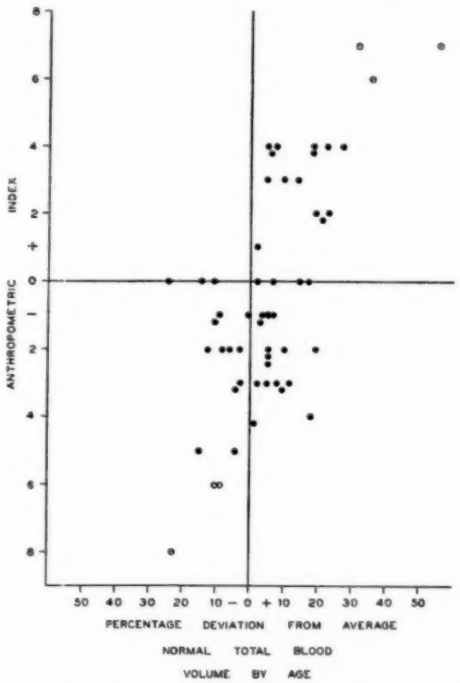

Fig. 4.—The relationship of total blood volume to conformity with anthropometric norms. The derivation of the anthropometric index is explained in the text. The fifty normal cases are represented by the solid circles. There is a general tendency for the larger children to have volumes above and for the small children to have volumes below the average value for a given age. This tendency is even more marked in the six children, represented by open circles, whose physical measurements were outside the accepted anthropometric norms.

assigned the values of +1, +2, and +3 for those of our cases coinciding with the fractions 25, 15, and 10 per cent above the mean, and –1, –2, and –3 for those coinciding with the corresponding fractions below the mean. These numerical indices are listed in Table I. The algebraic sum of these indices, which we call an anthropometric index, serves as an indication as to whether a child is tall, short, light, or heavy for his age.

An analysis of the percentage deviation from average total blood volume for age in relationship to these anthropometric indices is presented in Fig. 4. It is apparent that for any age absolute total blood volume is below average value in short, light children and above average in those who are tall and heavy.

Also included in this analysis are the six cases whose height or weight were well beyond the norms for age. It will be noted that those with high numerical indices have volumes which are farther above average value for age than any of the normal group, while the reverse is true of those with the low numerical indices.

We believe that height is the best correlation factor for prediction of volume because it is the least changeable of the three physical measurements. In pathologic cases in which malnutrition, dehydration, or edema are present, weight and hence surface area would give a false index. Then again, height is an easier measurement to obtain than weight in very sick children.

Actual plasma and total blood volume may be within plus or minus 15 per cent of the predicted value in about three quarters of all cases, and for practical purposes this range is accurate enough. Since the range of variation is about the same in all age groups, the agreement between actual and predicted volume is better in small children and infants than larger children, since the absolute error becomes less as the total blood volume diminishes.

The observations reported suggest that the optimal amount of and rate at which fluids or whole blood should be given intravenously should not be based upon a constant value (in terms of cubic centimeters per kilogram of body weight) but be estimated with relation to the normal plasma and total blood volume. This matter is being further investigated and will be reported upon later.

CONCLUSIONS

1. Plasma, red cell, and total blood volume were determined in nine infants and forty-one children between the ages of 2 and 17 years.

2. Total blood volume is about 300 c.c. at birth, doubles during the first year of life, and thereafter increases at the same rate in both sexes until puberty, when it is about 2,500 c.c. Thereafter, the volume of males increases more rapidly than that of females, and, when maximum growth is attained, is at the same level as that of adults of equivalent physical measurements.

3. Both plasma and total blood volume are more closely related to physical size than to age, and at any given age there is a direct parallel between the conformance to average normal volume values and average anthropometric measurements.

4. Unit volume in terms of plasma or whole blood per centimeter, kilogram, or square meter is not a constant but increases with continuing growth.

5. Normal plasma, red cell, and total blood volume may be predicted on the basis of height, weight, or surface area throughout infancy or childhood with a degree of accuracy sufficient for practical purposes. For clinical reasons we suggest that height is the correlative factor of choice.

NOTE: Since the acceptance of this paper for publication, an article by Schlutz and his associates has appeared in the JOURNAL OF PEDIATRICS, in which the results of blood volume studies in young negro boys were reported. These results correspond excellently with the results we obtained in a similar age group. These workers used essentially the same method employed by us, and the conformity of their results with ours constitutes a corroboration of our work.

The authors wish to express their appreciation for cooperation extended to them in this study at the Massachusetts General Hospital, the House of the Good Samaritan, the Long Island Hospital, Boston, and Phillips Andover Academy. Miss Evelyn Berstein rendered valuable technical assistance.

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SULFONAMIDE DRUGS IN THE TREATMENT OF EXPERIMENTAL DYSENTERY INFECTION IN MICE

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IN PREVIOUS studies[1] we found that all mice survived one minimum fatal dose of *Shigella paradysenteriae* Flexner suspended in mucin provided they were given a complete diet ad libitum containing 1 per cent of sulfathiazole* for two days or more before the culture was injected intraperitoneally. Many mice died when injected first with the culture and then placed on the 1 per cent "drug diet." Such mice became sick quickly, did not eat or ate very little, and as a result obtained an inadequate supply of the drug. We then began administering the drug by stomach tube in order to be certain of the drug intake. Injected mice usually became sick quickly and within five to six hours offered little resistance to handling. Most of these mice, when given 2 mg. of sulfathiazole by a stomach tube, became alert within thirty minutes; their toxemia disappeared; and they began moving about and eating. Such mice recovered. Other mice which failed to respond in this way died. With these favorable indications of the therapeutic efficiency of sulfathiazole, experiments were planned to obtain information regarding the therapeutic value of four sulfonamide compounds—sulfathiazole, sulfapyridine, sulfanilamide, and sulfamethylthiazole.

METHODS

Twenty-hour-old brain heart infusion broth (Difco) cultures of *S. paradysenteriae* were used throughout these studies. They were diluted serially in 3 per cent sterile mucin freshly prepared. One-half cubic centimeter of the proper dilution was injected intraperitoneally into each of the mice soon after making the dilution. One-half cubic centimeter of the highest dilution which killed all of ten mice was considered to contain one minimum fatal dose.

The white mice were obtained from one source, were weighed individually the day of the experiment (the weight range was limited between 16 and 20 Gm. each), and were selected so as to have all groups of ten mice comparable as to weight.

Mucin† was used as a 3 per cent sterile, freshly prepared solution in order to enhance the virulence of the cultures being studied. In the preparation of the mucin the proper amount was moistened with water and allowed to stand for ten minutes, after which it was ground in a mortar with the occasional addition of a few cubic centimeters of water until a smooth solution was obtained. After standing thirty minutes, it was autoclaved for fifteen minutes at 15 pounds pressure. It was then titrated, as soon as cool, and adjusted to pH 7.5.

From The Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.

*Sulfathiazole was supplied by E. R. Squibb and Son.

†Granular Type 1701-W. The Wilson Laboratories, Chicago, Ill.

The virulence of cultures was greatly increased by the presence of mucin. Broth cultures usually had a minimum fatal dose of 0.5 c.c. of a dilution of 1:100 or 1:1,000; however, the same cultures, in the presence of mucin, would have such an enhanced virulence that one minimum fatal dose might become 0.5 c.c. of dilutions of 10^{-5}, 10^{-9}, or greater. In a review of the literature we were unable to find any reference to in vivo sulfonamide studies with *Shigella paradysenteriae* Flexner, probably, as indicated by one author,[2] because of their slight virulence in broth.

The number of bacteria injected into the mice in each experiment was determined by making plate counts. This number varied but was usually between 200 and 2,000.

The pooled blood of two sacrificed mice was used for each determination of the concentration of drug in their blood. Marshall's method was used for the determinations.*

The sulfonamide compounds were suspended in sterile 3 per cent freshly prepared mucin. Mucin was used because of its convenience, since we were using it daily. A blunt 18 gauge, 1.5 inch needle attached to a 2 c.c. syringe was used for administering the drugs into the stomachs of the mice. The drug and mucin in the syringe were rotated frequently so as to maintain a uniform suspension of the drug. The mouse was held in the horizontal position, abdomen up, and the needle was passed easily and quickly through the mouth into the stomach, where 0.5 c.c., the amount containing the required dose, was injected. In each experiment the quantity of drug in mucin was checked by the method of Marshall. The calculated and actual quantities of drug always approximated each other closely.

Peritoneal fluid was obtained for bacterial counts by first cleansing the surface of the abdomen with alcohol, puncturing through into the peritoneal cavity with a sterile, calibrated capillary pipette, and withdrawing 0.01 c.c. of peritoneal fluid.

Blood for bacterial counts was obtained from the tail after cleansing the end with alcohol, then clipping it, and drawing up 0.01 c.c. into another sterile capillary pipette. Dilutions were then made, plated, and counted. A proportional number of colonies were picked and identified in order to be certain of the organism with which we were working.

DRUG DOSAGE

Our first experiments indicated that a single dose of 10 mg., 5 mg., or 2 mg. of sulfathiazole, administered by stomach tube three hours after injection of the culture and mucin, protected all mice against one minimum fatal dose. Other experiments showed that a single dose of 1 mg. was near the lower limit of the drug dose which usually protected. Doses of 1 and 2 mg. were chosen for use in the experiments reported here. All treated mice which survived were observed for thirty days, and all remained normal during that time.

DATA

An early experiment (Table I) showed that one dose of 2 mg. of sulfathiazole protected fifty-nine of sixty mice against 2 minimum fatal doses of Shigella paradysenteriae Flexner regardless of whether it was administered one, two, or three hours before or after injection of the culture and mucin. On the other hand, as seen in the same table, 2 mg. of sulfanilamide protected only five of thirty mice when administered one, two, or three hours before the culture and protected sixteen of thirty

*All drug tests were performed by Miss Dolores Kaely.

mice when administered one, two, or three hours after the culture. Twenty control mice which were injected with one minimum fatal dose died. These results indicated that 2 mg. of sulfathiazole would protect completely if it were administered either three hours before or after injection of two minimum fatal doses of culture, while sulfanilamide protected only six of twenty mice under similar conditions.

TABLE I

SHIGELLA PARADYSENTERIAE FLEXNER

EFFECTIVENESS OF ONE DOSE OF 2 MG. OF SULFATHIAZOLE OR SULFANILAMIDE BY STOMACH TUBE 1, 2, OR 3 HOURS BEFORE AND AFTER INJECTION OF 2 M. F. D. OF CULTURE AND MUCIN

MICE	HOURS TREATED	DEATHS			
		SULFATHIAZOLE		SULFANILAMIDE	
		BEFORE	AFTER	BEFORE	AFTER
40*	1	0	0	7	4
40	2	1	0	10	4
40	3	0	0	8	6
		1	0	25	14

*Ten mice were used in each group.
Each of twenty controls was given 1 M. F. D.; all died.

TABLE II

SHIGELLA PARADYSENTERIAE FLEXNER

EFFECTIVENESS OF ONE DOSE OF 2 MG. OF SULFATHIAZOLE BY STOMACH TUBE TWO HOURS BEFORE, AT THE SAME TIME, OR THREE HOURS AFTER INJECTION OF CULTURE AND MUCIN

MICE	MINIMUM FATAL DOSES	DEATHS			
		2 HOURS BEFORE	SAME TIME	3 HOURS AFTER	%
30*	10	0	0	0	0
30	100	3	0	0	10
30	1,000	2	0	5	23
30	10,000	10	4	7	70
30	100,000	10	10	10	100
		25	14	22	

*Ten mice were used in each group.
Each of ten controls was given 1 M. F. D.; all died.

When 2 mg. of sulfathiazole were administered two hours before, at the same time, or three hours after ten minimum fatal doses of the injected culture (Table II) all of the thirty mice were protected. Twenty-seven of thirty mice treated similarly were protected against 100 minimum fatal doses, and twenty-three of thirty mice were protected against 1,000 minimum fatal doses. Only nine of thirty mice survived 10,000 minimum fatal doses, and none were protected against 100,000 minimum fatal doses.

The results in Tables I and II led naturally to the question of how long after injection of the culture administration of the drug could be delayed and therapeutic effects could still be expected. The data in

Table III are those obtained in an experiment so planned that there could be noted the effect of delaying treatment with one and two doses of 2 mg. of each of two drugs, sulfathiazole and sulfanilamide. The single doses of the two drugs were administered to separate groups of ten mice three, five, eight, ten, and twelve hours after the injection of one minimum fatal dose of the culture. In that portion of the experiment in which groups of ten mice were treated with two doses of the drugs, the first dose of drug was administered six, eight, ten, and twelve hours after injection of the culture. Each group received their second dose three hours after the first. The mortality was lower among the mice treated with two doses of the drugs; that is, 25 per cent mortality with two doses of sulfathiazole as compared to 40 per cent with one dose,

TABLE III

SHIGELLA PARADYSENTERIAE FLEXNER

EFFECTIVENESS OF ONE AND TWO DOSES OF 2 MG. OF SULFATHIAZOLE AND SULFANILAMIDE BY STOMACH TUBE AT VARIOUS HOURS AFTER INJECTION OF 1 M. F. D. OF CULTURE AND MUCIN

MICE	ONE DOSE, HOURS	DEATHS		% DIED	TWO DOSES, HOURS	DEATHS		% DIED
		SULFATHIAZOLE	SULFANILAMIDE			SULFATHIAZOLE	SULFANILAMIDE	
20*	3	0	4	20				
40	5	1	2	15	6, 9	0	0	0
40	8	6	9	75	8, 11	1	6	35
40	10	6	10	80	10, 13	3	7	50
40	12	7	9	80	12, 15	6	7	65
		20 (40%)	34 (68%)			10 (25%)	20 (50%)	

*Ten mice were used in each group.
Each of twenty-four controls was given 1 M. F. D.; twenty-three died.

and 50 per cent with two doses of sulfanilamide as compared to 68 per cent with one dose. Also the mortality was lower with the two doses at each interval of time after injection of the culture as is seen by comparing, for instance, the 15 per cent mortality for one dose at five hours with no mortality for two doses at six and nine hours. It is interesting to point out that there was little difference in the mortality among the "single dose" groups at eight, ten, and twelve hours after injection of the culture, the mortality being 75, 80, and 80 per cent respectively. As might be expected, among the two dose groups treated with sulfathiazole there was a progressive increase in the mortality with delay in instituting therapy, and yet the total mortality (25 per cent) was lower than with the single dose groups (40 per cent). Among the two dose groups treated with sulfanilamide there was slight difference in mortality when therapy was instituted at eight, ten, and twelve hours. Fig. 3 shows that the mice were heavily infected at eight hours since the bacterial counts on peritoneal fluids of untreated mice at this time were about 100,000,000 per cubic centimeter and the counts on blood at the same time were about 1,000,000 per cubic centimeter. At ten and twelve hours the bacterial counts were considerably higher, and some mice

died as early as twelve hours after infection. This protection with a drug at these late hours is a striking result and indicates, in a remarkable way, the ability of the drugs to bring about a change resulting not only in a cessation in the rapid multiplication of overwhelming numbers of bacteria but also the death of all of the bacteria in vivo.

In subsequent experiments single doses of the drugs were administered three hours after injection of the culture. This time interval was adopted because it allowed time for the mice to become sick and was a more severe test on the therapeutic value of the drug.

TABLE IV

SHIGELLA PARADYSENTERIAE FLEXNER

EFFECTIVENESS OF 1 MG. OF FOUR SULFONAMIDE COMPOUNDS GIVEN BY STOMACH TUBE THREE HOURS AFTER INJECTION OF CULTURE AND MUCIN

MICE	MINIMUM FATAL DOSES	DEATHS				
		SULFATHIAZOLE	SULFAPYRIDINE	SULFANILAMIDE	SULFAMETHYLTHIAZOLE	%
40*	1	0	0	2	0	5
40	10	2	0	6	1	22
40	100	4	6	9	8	68
40	1,000	10	10	10	10	100
		16	16	27	19	

*Ten mice were used in each group.

The therapeutic efficiency of one dose of 1 mg. of sulfathiazole, sulfapyridine, sulfanilamide, and sulfamethylthiazole against 1, 10, 100, and 1,000 minimum fatal doses is obvious in Table IV. It is observed that, of forty mice injected with one minimum fatal dose, all of ten treated with sulfathiazole survived as did also all of ten treated with sulfapyridine and sulfamethylthiazole, while two of the ten treated with sulfanilamide died. Nine of forty mice which were injected with 10 minimum fatal doses died; twenty-seven of the forty injected with 100 minimum fatal doses died; and all forty injected with 1,000 minimum fatal doses died. Sulfanilamide offered less protection than did the other three drugs, and this was true in several experiments. The other three drugs offered considerable protection against ten minimum fatal doses, while two, sulfathiazole and sulfapyridine, protected 50 per cent of the mice against 100 minimum fatal doses; the other two drugs protected only three of twenty mice against the same amount of culture.

It was felt that repetition of the drug doses at frequent intervals might result in greater protection to the infected mice. Accordingly 2 mg. of the four sulfonamide compounds were administered by stomach tube every three hours for thirty-six hours following the injection of culture and mucin. In Table V it is observed that thirty-eight of forty treated mice survived five minimum fatal doses, and thirty-eight of forty untreated mice died; thirty-nine of forty treated mice survived fifty minimum fatal doses, and thirty-six of forty untreated mice died;

only thirteen of forty treated mice survived 500 minimum fatal doses, while all forty untreated mice died; and one of forty treated mice survived 5,000 minimum fatal doses, while all of forty untreated mice died. Tables IV and V cannot be compared directly, since the drug dose and the minimum fatal dose are not the same, being a single dose of 1 mg. and repeated doses of 2 mg., respectively, and 1 and 5 minimum fatal doses, respectively. The data indicate, however, that repeated doses of 2 mg. of the four drugs only protected against five times as many minimum fatal doses as did 1 mg. It might seem that greater protection should follow drug administration every three hours with its resultant maintenance of a higher blood drug concentration. However, later experiments (Fig. 3) indicated that one dose of 2 mg. of sulfathiazole in mice injected with one minimum fatal dose resulted in a complete disappearance of the bacteria in the blood stream and peritoneal fluid with recovery of the mice. Thus it would appear that, in such animal experiments as these, repeated doses of the four drugs could not offer much more protection than did one dose.

TABLE V

SHIGELLA PARADYSENTERIAE FLEXNER

EFFECTIVENESS OF REPEATED DOSES OF 2 MG. OF FOUR SULFONAMIDE COMPOUNDS BY STOMACH TUBE EVERY THREE HOURS FOR THIRTY-SIX HOURS; FIRST DOSE THREE HOURS AFTER INJECTION OF CULTURE AND MUCIN

MICE	MINIMUM FATAL DOSES	DEATHS					CONTROL NO.	MICE DIED
		SULFATHIAZOLE	SULFAPYRIDINE	SULFANILAMIDE	SULFAMETHYLTHIAZOLE	%		
40*	5	1	0	0	1	5.0	40	38
40	50	1	0	0	0	2.5	40	36
40	500	9	5	9	4	67.0	40	40
40	5,000	10	10	9	10	97.0	40	40
		21	15	18	15			

*Ten mice were used in each group.

The previous experiments indicated that sulfathiazole, sulfapyridine, and sulfamethylthiazole were of definite therapeutic value in the treatment of mice experimentally infected with the Flexner type of *Shigella paradysenteriae*. Tables VI, VII, and VIII contain data regarding the therapeutic value of the same sulfonamide compounds in experimental infections in mice due to the Sonne type of dysentery bacilli. In Table VI it is seen that sulfathiazole is of greatest therapeutic value protecting thirty mice—10 each, against 10, 100, and 1,000 minimum fatal doses when administered immediately after injection of the culture. It was next most effective when administered two hours before the culture, at which time it protected twenty-five of thirty mice. It was almost as effective three hours after injection of the culture when it protected twenty-two of thirty mice.

The therapeutic value of the four sulfonamide compounds is presented in Table VII for mice infected with the Sonne type of dysentery bacilli. This table may be compared with Table IV, which contains data from a similar experiment in which a Flexner culture was used.

TABLE VI

SHIGELLA PARADYSENTERIAE SONNE (CHEAT)

EFFECTIVENESS OF ONE DOSE OF 2 MG. OF SULFATHIAZOLE BY STOMACH TUBE TWO HOURS BEFORE, AT THE SAME TIME, OR THREE HOURS AFTER INJECTION OF CULTURE AND MUCIN

MICE	MINIMUM FATAL DOSES	DEATHS		
		2 HOURS BEFORE	SAME TIME	3 HOURS AFTER
30*	10	0	0	1
30	100	0	0	0
30	1,000	5	0	7

*Ten mice were used in each group.
Each of ten controls was given 0.1 M. F. D.; two died.
Each of ten controls was given 1.0 M. F. D.; all died.

TABLE VII

SHIGELLA PARADYSENTERIAE SONNE (CHEAT)

EFFECTIVENESS OF ONE DOSE OF FOUR SULFONAMIDE COMPOUNDS GIVEN BY STOMACH TUBE THREE HOURS AFTER INJECTION OF CULTURE AND MUCIN

MICE	MINIMUM FATAL DOSES	DEATHS				
		SULFATHIAZOLE 1 MG.	SULFAPYRIDINE 1 MG.	SULFANILAMIDE 2 MG.	SULFAMETHYLTHIAZOLE 1 MG.	%
40*	1	1	1	2	1	12
40	10	5	4	7	2	45
40	100	6	6	10	6	70
40	1,000	6	7	10	10	82
40	10,000	10	10	10	10	100
		28	28	39	29	

*Ten mice were used in each group.
Each of twenty controls was given 1 M. F. D.; all died.

TABLE VIII

SHIGELLA PARADYSENTERIAE SONNE (WMS.)

EFFECTIVENESS OF ONE DOSE OF 2 MG. OF SULFATHIAZOLE BY STOMACH TUBE THREE HOURS AFTER INJECTION OF CULTURE AND MUCIN

MICE	MINIMUM FATAL DOSES	SULFATHIAZOLE, 2 MG. DEATHS
10	1	0
10	10	3
10	100	7
10	1,000	9
10	10,000	10

Each of ten controls was given 1 M. F. D.; all died.

The results in the two experiments are more or less similar, indicating that the four drugs are about equally efficient therapeutically in both the Flexner and Sonne types of experimental infections in mice.

In Table VIII a different Sonne culture was used to test the value of sulfathiazole, and good results were again obtained which were similar to those with the first Sonne culture.

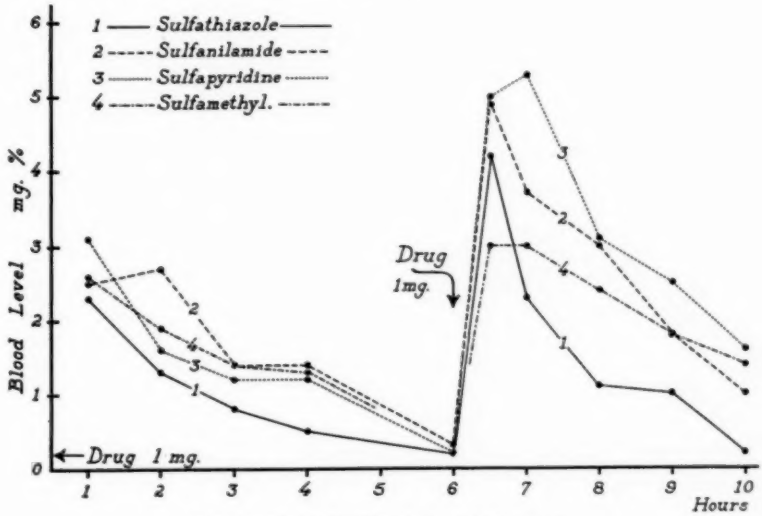

Fig. 1.—Blood drug levels in infected mice.

The blood drug levels for the four sulfonamide compounds in infected mice are plotted in Fig. 1. Each blood level determination was obtained on the pooled blood of two sacrificed mice. In this experiment the mice were first given 1 mg. of each of the four drugs three hours after injection of the culture. One hour later and each hour thereafter for six hours blood was obtained for determining the drug concentration. At the end of six hours, when the blood level in each instance was almost negligible, the mice were given another 1 mg. of each drug. Blood was then obtained thirty minutes later, one hour after administration, and hourly for the next three hours. Two of the drugs, sulfapyridine and sulfanilamide, gave higher blood levels one hour after the second administration of drug than was the case one hour after the first drug dose. Slightly higher blood levels were maintained following the second administration except in the case of sulfathiazole.

In Fig. 2 the blood drug levels are plotted for normal mice receiving 1 and 2 mg. of the four sulfonamide compounds. One milligram of two of the drugs gave blood levels of 3 and 5 mg. per cent in one-half hour. The other two drugs were not tested at this time. The 2 mg. doses gave levels of 6.5 to 9.0 mg. per cent in one-half hour. The 2 mg. doses maintained a higher level over four hours than did 1 mg.

Bacterial counts were made on the peritoneal fluid and blood of treated and untreated mice in order to obtain information regarding the number

of bacteria. In the case of two infected mice not treated with drug (Fig. 3) the counts on the peritoneal fluid increased rapidly until the time of death at twelve and fourteen hours. The counts are charted as the logarithms of the number of bacteria. The number of viable bacteria in the blood paralleled the increase in the peritoneal fluid but was always considerably less. It is therefore apparent that, after an early invasion of the blood stream, the bacteria increased rapidly in number in both peritoneal fluid and blood to such a degree that they overwhelmed and killed the mice within twelve to fourteen hours.

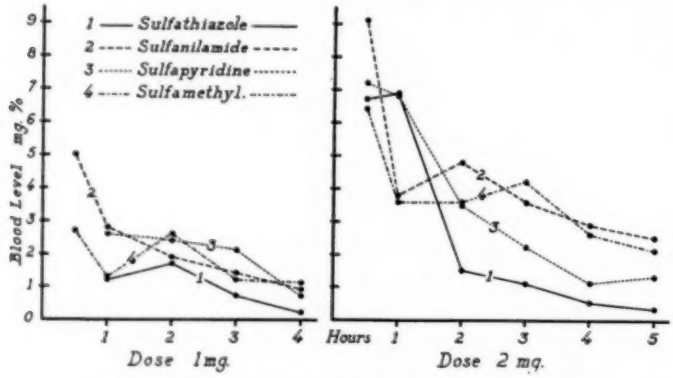

Fig. 2.—Blood drug levels (mg. per cent) in normal mice.

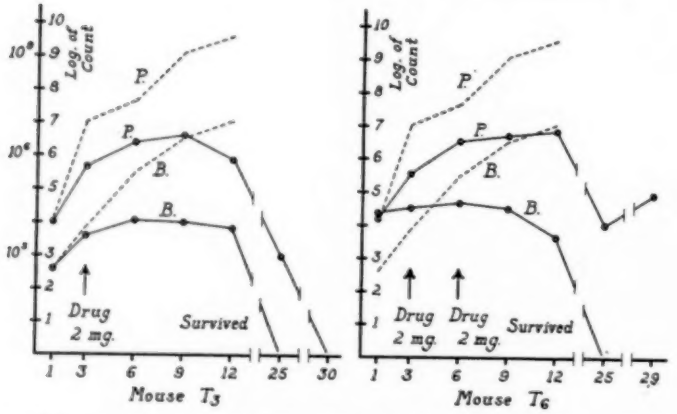

Fig. 3.—Bacterial counts on peritoneal fluid and blood. Dotted lines represent untreated mice, which died; solid lines, treated mice which survived.

Fig. 3 demonstrates what happened to the bacteria in the infected mice which were treated with one or two doses of 2 mg. of sulfathiazole. The dotted lines indicate the bacterial counts of the peritoneal fluid and blood of two untreated mice; the solid lines indicate corresponding

bacterial counts in two treated mice. It is apparent that the early bacterial increase slowed down for six hours following administration of the drug and then rapidly decreased to zero in twenty-five to thirty hours, and the mice survived. Again the number of bacteria in the blood paralleled, but was always less than, the number in the peritoneal fluid. We have no further information at present regarding the mode of destruction of these bacteria in vivo.

CONCLUSIONS

Mucin greatly enhances the virulence of cultures of *Shigella paradysenteriae* Flexner and Sonne.

Administration of sulfonamide compounds to mice by stomach tube is an easy and rapid method for assuring the required dosage of drugs.

Sulfathiazole gave complete protection against the injection into mice of two minimum fatal doses of *Shigella paradysenteriae* Flexner when administered either three hours before or after the culture.

Over a range of increasing multiples of minimum fatal doses, sulfathiazole is of most value when given immediately after the culture and is next most effective when given three hours after the culture.

Study of delayed treatment with one and two doses of 2 mg. of sulfathiazole and sulfanilamide in mice infected with one minimum fatal dose indicated that two doses three hours apart were of more value than one dose and that one and two doses offered considerable protection when administered eight and twelve hours respectively after injection of culture.

Sulfathiazole, sulfapyridine, and sulfamethylthiazole were about equally efficient as therapeutic agents, and sulfanilamide was usually of least value.

Repeated doses of the four sulfonamide compounds every three hours for thirty-six hours did not offer much more protection than a single dose three hours after the culture.

Blood concentrations in infected mice one hour after administration of 1 mg. of the four sulfonamide compounds varied between 2 and 3 mg. per cent, and one-half hour after a second dose varied between 3 and 5 mg. per cent. In normal mice 2 mg. of the drugs resulted in blood levels between 6 and 9 mg. per cent one-half hour after administration of the drug.

The bacteria increased in the peritoneal fluid of mice, not treated with a sulfonamide compound, from 10,000 at one hour after injection to 1 to 10 billion within twelve to fourteen hours, at which time the mice died. The number of bacteria increased in the blood of the same mice from 1,000 per cubic centimeter at one hour after injection to 1 to 10 million per cubic centimeter at the time of death in twelve to fourteen hours.

There was only a slight increase for three to six hours in the number of bacteria in the peritoneal fluid and blood of infected mice after administration of sulfathiazole, then a rapid decrease to zero in twenty-five to thirty hours or longer, with survival of the mice.

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SULFATHIAZOLE THERAPY OF INFANTILE DIARRHEA

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EVERY other patient (or thirteen) of the twenty-seven children admitted to Duke Hospital between July 15 and Nov. 15, 1940, because of parenteral diarrhea or bacillary dysentery was treated with sulfathiazole* in initial oral doses of 1 Gm. (gr. xv) per year of age up to a maximum of 3 Gm. (gr. xlv), followed by the same daily amount divided in six doses. The alternate fourteen patients were the controls. Six of the latter also received sulfathiazole late in their course. Except for the sulfathiazole, the treatment† was the same in the two groups. As may be seen in Table I, the patients in the two groups were comparable in regard to age, seasonal incidence, severity, intoxication, type of infection, number and character of stools, and laboratory studies.‡

The four following case reports are examples of the patients in the two groups. Patient 2 who was treated with sulfathiazole and patient 14 of the control group who did not receive sulfathiazole until late in her course were brother and sister, aged 2 and 3 years, respectively. The stool cultures in both cases were positive for Flexner Y dysentery bacilli, and both patients' serum agglutinated 1:1,280 for Flexner Y. Four days prior to admission the brother had a sudden onset of diarrhea, with ten to twelve greenish, watery stools which subsequently showed gross blood. The patient took little food or fluid; he had had fever since onset. Two days later the 3-year-old sister had a sudden onset of diarrhea, with fifteen green, watery, and bloody stools. Upon

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*Thanks are due Merck & Company and Winthrop Chemical Company for supplying the sulfathiazole.

That sulfathiazole has in vitro activity against the colon-typhoid-dysentery group of organisms was shown by the following reports: Lawrence, C. A.: Bacteriostatic Effect of Sulfanilamide, Pyridine, and Thiazole Derivatives Upon Colon-Typhoid-Dysentery Group, Proc. Soc. Exper. Biol. & Med. 44: 162, 1940; Libby, R. L., and Joyner, H. L.: The Action of Sulfathiazole on the Colon-Typhoid-Dysenteriae Group of Organisms, J. Infect. Dis. 67: 67, 1940.

†The routine basic treatment which all diarrhea patients received was: (1) Oral, subcutaneous, and intravenous ⅙ molar sodium lactate as indicated; (2) five per cent dextrose intravenously, not more than 30 c.c. of fluid intravenously per kilogram of body weight, used as indicated; (3) parenteral fluids to combat dehydration; (4) blood transfusions following hydration, if indicated; (5) nothing by mouth for the first twenty-four hours except Ringer's solution with saccharin ad lib. and weak tea ad lib.; (6) after the initial fast, a formula of equal parts of evaporated milk and water with 0.75 per cent lactic acid and 5 per cent casec was offered in amounts furnishing 20 calories per kilogram of body weight, and if this was taken, the quantity was increased by 20 calories per kilogram every second day until the caloric requirements were attained; (7) daily maintenance parenteral doses of thiamin chloride and ascorbic acid.

‡The following routine laboratory studies were made: (1) Stool culture for three successive days; (2) plasma carbon dioxide combining power on admission; (3) three negative stool cultures before discharge; (4) agglutination tests of the patient's serum for the typhoid, paratyphoid, and dysentery groups after ten days or just prior to discharge.

TABLE I

CASE NO.	SEX, RACE, AGE (YR.)	DURATION OF DIARRHEA PRIOR TO ADMISSION (DAYS)	NUMBER OF STOOLS BEFORE ADMISSION (DAILY)	CHARACTER OF STOOLS[a]	DEGREE OF DEHYDRATION	APPRAISAL OF CASE	CO_2 ON ADMISSION (VOLS. %)	DURATION OF DIARRHEA AFTER ADMISSION[c] (DAYS)	DAYS DRUG GIVEN	STOOL CULTURES	DIAGNOSIS
Group I. Thirteen Patients Treated With Sulfathiazole											
1	M, W, 9/12	21	20-30	M	Mkd.	Severe	31[b]	2	6	Negative	Parenteral diarrhea
2	M, W, 2	4	6-8	MB	Mkd.	Severe	41[b]	3	6	Flexner Y	Bacillary dysentery
3	F, W, 2 5/12	1	8-10	M	0	Mild	48	3	5	Negative	Parenteral diarrhea
4	M, C, 4/12	5	8-10	MB	Mod.	Mod.	48	6	8	Flexner Z	Bacillary dysentery
5	F, W, 2 5/12	2	12-15	MB	Mod.	Severe	33[b]	3	4	Negative	Diarrhea—cause ?
6	M, W, 9/12	7	15-20	MB	Mkd.	Severe	30[b]	4	6	Negative	Parenteral diarrhea
7	F, W, 7/12	21	6-8	M	Mkd.	Mod.	38[b]	3	5	Negative	Diarrhea—cause ?
8	F, W, 11/12	21	10-18	MB	Mild	Mod.	50	4	5	Flexner W	Bacillary dysentery
9	F, W, 2/12	2	9-10	M	Mkd.	Mod.	23[b]	2	4	Negative	Diarrhea—cause ?
10	F, W, 3/12	2	6-8	MB	Mild	Mild	Not done	2	5	Negative	Parenteral diarrhea
11	M, C, 6/12	8	11-12	M	Mod.	Mod.	40	4	8	Negative	Parenteral diarrhea
12	F, W, 11/12	28	6-8	MB	Mkd.	Severe	45	4	6	Negative	Diarrhea—cause ?
13	M, C, 3	1	6-7	MB	Mod.	Mod.	32[b]	2	3	Flexner Y	Bacillary dysentery
Group II. Fourteen Patients Admitted Alternately to Those in Group I and Not Treated With Sulfathiazole[d]											
14	F, W, 3	2	60-70	MB	Mkd.	Severe	31[b]	6	4-9	Flexner Y	Bacillary dysentery
15	F, C, 2	3	6-20	MB	Mkd.	Severe	25[b]	9		Flexner W	Bacillary dysentery
16	F, C, 4/12	4	15	MB	Mod.	Mod.	39	27	4th	Flexner Z	Bacillary dysentery[e]
17	M, C, 11/12	42	8-12	M	Mkd.	Severe	30[b]	12		Negative	Parenteral diarrhea
18	M, W, 9/12	9	20-30	MB	Mkd.	Severe	37[b]	10		Negative	Diarrhea—cause ?
19	F, W, 1/12	8	8-10	MB	Mkd.	Severe	32[b]	32	28-32	Negative	Diarrhea—cause ?
20	M, W, 8/12	4	10-20	MB	Mod.	Mod.	40[b]	12	10-15	Flexner V	Bacillary dysentery
21	M, W, 3/12	21	5-20	MB	Mod.	Mod.	38	40		Negative	Parenteral dysentery
22	F, C, 1 6/12	5	8-10	MB	Mkd.	Severe	22[b]	21		Flexner W	Bacillary dysentery
23	M, W, 1	6	8-9	M	Mod.	Mod.	37[b]			Negative	Diarrhea—cause ?[f]
24	F, W, 5/12	18	20	B	Mod.	Mod.	38	15	9-15	Negative	Diarrhea—cause ?
25	M, W, 5/12	12	6-8		0	Mild	67	12		Negative	Diarrhea—cause ?
26	F, W, 5/12	7	10		0	Mild	64	6	4-7	Negative	Diarrhea—cause ?
27	M, W, 1	30	6-25	MB	Mod.	Mod.	35[b]	17		Negative	Parenteral diarrhea

[a]M, Mucous; B, bloody.
[b]Received 1/6 molar sodium lactate.
[c]Determined when stools reached four daily.
[d]Except Patients 14, 16, 19, 20, 24, and 26, who were given sulfathiazole late in the course of disease.
[e]Died.
[f]Died nine hours after admission.

admission the brother appeared markedly ill and dehydrated. The sister did not appear ill. The temperature course of both patients is depicted in Fig. 1.

The brother's plasma carbon dioxide combining power was 41 volumes per cent. He was given molar sodium lactate and hydrated. Two grams of sulfathiazole were given immediately and 0.5 Gm. every six hours. Forty-eight hours later his temperature was normal and his stools were semisolid and three in number. He had taken weak tea and Ringer's solution with saccharine avidly up until this time. He then was given 60 c.c. lactic acid evaporated milk with 5 per cent casec every four hours. The sulfathiazole was discontinued on the sixth day and the child made an uneventful recovery.

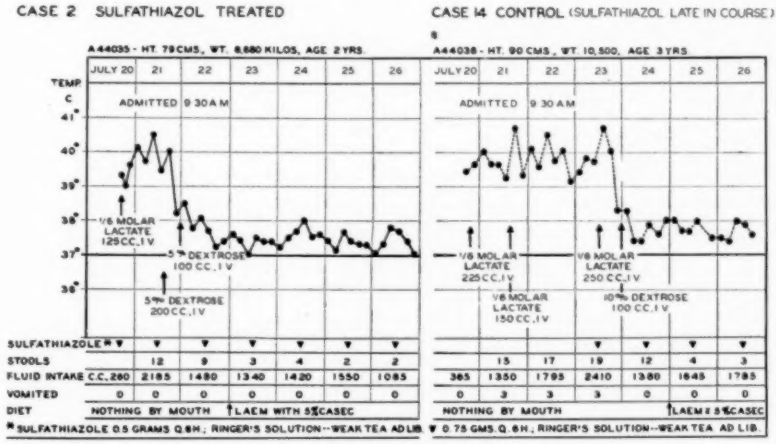
CASE 2 SULFATHIAZOL TREATED
A44035 - HT. 79 CMS., WT. 8,880 KILOS, AGE 2 YRS.
JULY 20 21 22 23 24 25 26
TEMP C
ADMITTED 9 30 A.M.
1/6 MOLAR LACTATE 125 CC. I.V.
5% DEXTROSE 100 CC. I.V.
5% DEXTROSE 200 CC. I.V.
SULFATHIAZOLE* ▼ ▼ ▼ ▼ ▼ ▼ ▼
STOOLS 12 9 3 4 2 2
FLUID INTAKE C.C. 260 2185 1480 1340 1420 1550 1085
VOMITED 0 0 0 0 0 0 0
DIET NOTHING BY MOUTH ↑LAC-M WITH 5% CASEC
*SULFATHIAZOLE 0.5 GRAMS Q.6H.; RINGER'S SOLUTION--WEAK TEA AD LIB.
CASE 14 CONTROL (SULFATHIAZOL LATE IN COURSE)
A44038 - HT. 90 CMS., WT. 10,500, AGE 3 YRS.
JULY 20 21 22 23 24 25 26
ADMITTED 9 30 A.M.
1/6 MOLAR LACTATE 225 CC. I.V.
1/6 MOLAR LACTATE 150 CC. I.V.
1/6 MOLAR LACTATE 250 CC. I.V.
10% DEXTROSE 100 CC. I.V.
▼ ▼ ▼ ▼ ▼ ▼
15 17 19 12 4 3
365 1350 1795 2410 1380 1645 1785
0 3 3 3 0 0 0
NOTHING BY MOUTH ↑LAC-M 5% CASEC
▼ 0.75 GMS. Q. 6H.; RINGER'S SOLUTION--WEAK TEA AD LIB.

Fig. 1.

The sister was placed on the diarrhea routine treatment* without sulfathiazole. Her temperature rose and the number of her stools increased. Her plasma carbon dioxide combining power was 31 volumes per cent. She became so ill that sulfathiazole was administered on the third day after admission. The following morning her temperature was normal and her stools were normal in twenty-four hours. Her course from this time was uneventful.

Patient 4 who was treated with sulfathiazole and Patient 16 of the control group were 4-month-old twins. Stool cultures were positive in both cases for Flexner Z. The boy had the sudden onset of diarrhea, with eight to ten green stools with much mucus five days before admission. His sister began having a diarrhea of "many" green stools one day later. Upon admission both patients looked acutely ill. The brother's temperature was 39.4° C. (103° F.) and his plasma carbon dioxide combining power was 48 volumes per cent; the sister's tem-

*See footnote†, page 469.

perature was 39.8° C. (103.8° F.) and her plasma carbon dioxide combining power was 39 volumes per cent. They were both hydrated and placed on the basic regime. The brother received 0.1 Gm. sulfathiazole every six hours. Twenty-four hours later his temperature was normal, and his stools became normal in number on the sixth hospital day. The sister's temperature remained elevated, numerous bloody green stools with much mucus persisted, and slight jaundice appeared. On the fourth hospital day she was given 0.9 Gm. sulfathiazole, but the jaundice increased and the drug was stopped. The frequency of stools persisted. She received numerous blood transfusions. She died on the twenty-seventh hospital day.

DISCUSSION

The average time required for the stools to reach four a day of normal color and consistency was 3.2 days in the sulfathiazole-treated group and 15.6 days in the control group. No deaths occurred in the sulfathiazole-treated group. Of the fourteen controls, two died, one after a protracted hospital course of twenty-seven days, and the other, nine hours after admission. In the sulfathiazole-treated group, the duration of diarrhea after admission bore no relation to the duration of diarrhea prior to admission; however, in the control group, recovery was later in those who had had prolonged diarrhea prior to admission.

The only reaction which could possibly be attributed to sulfathiazole was a slight increase in jaundice in one patient shortly after sulfathiazole was given. This child received 0.9 Gm. of the drug on the fourth hospital day. Although the sulfathiazole was discontinued immediately after the increase in jaundice, the jaundice persisted for several days. As the patient had received multiple transfusions prior to the administration of the drug, sulfathiazole may not have been responsible for the increase in the jaundice.

CONCLUSION

Sulfathiazole is effective in the treatment of children with parenteral diarrhea or bacillary dysentery, particularly the latter.

AN EVALUATION OF CONVALESCENT SERUM IN THE PREVENTION OF MUMPS

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RECENT reports on the use of convalescent serum in preventing mumps have been very favorable. Zeligs[1] reported 100 per cent success in forty-four boys, 10 to 18 years of age, using 5 c.c. convalescent serum. Regan[2] reported but one failure in seventy cases, using but 2 to 4 c.c. Kutscher[3] showed a 98-per-cent protective incidence in boys 9 to 16 years old, using 8 to 10 c.c. Skrotsky[4] reported two failures in 179 children, using 5 to 15 c.c.

Such reports prompted the use of serum at The Children's Hospital when a diabetic child developed mumps on his fifth hospital day, exposing several nurses and ward patients. From this beginning, an epidemic of thirty-five cases developed over a four months' period despite the liberal administration of convalescent serum and the usual isolation procedures. The fact that a great deal of faith was placed in serum at the beginning of the epidemic was partially responsible for its prolongation.

Serum was given to all known susceptible contacts. A total of eighty-six persons (fifty-nine children and twenty-seven adults) received serum as follows:

Fifty-five persons were exposed once and received 8 or 10 c.c. of serum. Four of this group developed mumps. (One, however, did not receive serum until twelve days after probable exposure.)

Four children were exposed twice, and they received 10 c.c. serum only after the first exposure. All developed mumps after a later second exposure.

Fifteen persons (ten nurses, five children) were exposed twice at seven- to thirty-four-day intervals and received 10 c.c. serum after each exposure. Two of the children developed mumps.

Six older boys were exposed once, and received 10 c.c. serum on the first and again on the ninth day after exposure. One of these developed mumps.

Six nurses were exposed once, and received 20 c.c. of serum the fourth day after exposure. None developed mumps.

Thus, of eighty-six persons receiving serum, eleven children contracted mumps, but no cases developed among adults.

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There were approximately seventy-five employees in the hospital who had never had mumps who did not receive serum because no contact with mumps was reported by them. Of this group, sixteen (21 per cent) developed mumps.

Eight cases of mumps developed in children who had not received serum. Some of these were the original cases before serum therapy was started. We have no control group among children.

Serum was obtained from young adults whose mumps had been severe and whose parotid swelling had been gone from one to five weeks. The serum was tested for syphilis and contamination, passed through a Zeiss filter, and refrigerated in 10-c.c. ampules until used.

When a case of mumps developed on a ward, the patient was removed to the isolation building. Those exposed susceptible patients and nurses were given 8 or 10 c.c. of serum intramuscularly within one to five days after exposure. The ward was closed to new admissions, and nurses who presumably were immune were put on duty. Despite such measures, failures in immunization and shifting of personnel allowed spread of the disease.

When the first failures with serum appeared, various methods of administering it were tried. Fifteen re-exposed, previously inoculated patients were given another dose of serum. In this group there were two failures. Also two injections of 10 c.c. each were given to six boys on the first and ninth days after exposure, with one failure. Six nurses received 20 c.c. of serum.

None of the cases in children were severe, and no difference in severity or duration of the mumps was noted between the inoculated and the untreated cases. As no inoculated adults developed mumps, no comparison can be made. No serum was used in treatment. There was a mild orchitis in a 16-year-old boy who had received serum. No other complications from mumps or serum occurred.

An analysis of the eleven failures follows:

CASE 1.—A 5-year-old boy received 8 c.c. of serum one day after exposure to mumps. He was re-exposed thirteen days later and developed mumps eighteen days after the second exposure.

CASE 2.—A 4-year-old girl received 8 c.c. of serum five days after her first exposure. Seventeen days later she was re-exposed and developed mumps nineteen days after the second exposure.

CASES 3 AND 4.—Two boys, 10 and 12 years old, received 10 c.c. of serum each one day after exposure. They were re-exposed five days after the serum was given and developed mumps nineteen and twenty days thereafter.

CASES 5 AND 6.—Two boys, each aged 4 years, received 8 c.c. of serum the day of exposure. Thirty-four days later they were again exposed and again received 10 c.c. of serum, but developed mumps twenty-one days after the second exposure.

Passive immunity is usually maintained with measles convalescent serum for from two to four weeks. These failures suggest either a very brief period of protection with mumps serum, or, as in Cases 3 and 4, a possible prolongation of the incubation period.

Cases 5 and 6 were two failures out of fifteen contacts who received serum after second exposures.

CASES 7 AND 8.—Two girls, aged 12 and 13 years, each received 10 c.c. of serum four days after exposure, but developed mumps on time, eighteen days after exposure. (Because of these two failures and Case 2, treated with the same serum, we suspected its potency; yet there were ten successes with the same lot.)

CASE 9.—A girl, aged 5 years, received 10 c.c. of serum the day after exposure, but developed mumps eighteen days later.

CASE 10.—A boy aged 16 years received 10 c.c. of serum the day of exposure and another dose nine days later, to make sure of immunity. He developed mumps, however, with a mild orchitis, eighteen days after the exposure. (Five other older boys were treated similarly, having been exposed under the same circumstances, and they did not develop mumps.)

CASE 11.—A boy, aged 9 years, received 10 c.c. of serum the day after exposure and developed mumps five days later. (It was assumed he had been previously exposed. This, therefore, was probably not a serum failure.)

SUMMARY

An experience with convalescent mumps serum is presented, in which there were eleven failures to prevent the disease after treating eighty-six exposed susceptible persons. Six of the failures occurred in children who had been re-exposed to the disease after having attained an apparent immunity to the first exposure.

While this is too small a group of cases from which to draw many conclusions, it may add to the experience of others in evaluating this form of therapy.

These data indicate that 10 c.c. of convalescent mumps serum gives a passive immunity of very short duration in a high percentage of cases, and that it seems necessary to repeat the injection of serum after each exposure to the disease.

Our experience suggests that previous reports on this subject have been too encouraging and that, while serum is of definite value, it should not be depended upon too strongly for the control of institutional epidemics.

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TREATMENT OF MEASLES WITH CONVALESCENT SERUM AND CONCENTRATED ADULT NORMAL SERUM

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I. CONVALESCENT SERUM IN PRE-ERUPTIVE AND ERUPTIVE MEASLES

IT HAS been shown by Levinson and Connor[1] and the authors[2] that measles can be modified if sufficient quantities of convalescent serum are given in the pre-eruptive stage. It was found that 40 to 50 c.c. given intravenously were necessary for such modification.

Since our last communication, we have given convalescent serum to five more patients during the pre-eruptive stage. In four of these patients, definite modification of the measles was obtained.

Guibert and Lapeyre[3] and Armstrong[4] have reported that the clinical course of measles was definitely improved when convalescent serum was given in the eruptive stage. This was noted especially in severely ill patients.

We attempted to confirm this observation. Eight children were given 40 to 105 c.c. of convalescent serum early in the eruptive stage. In only two of these eight patients were the measles considered to be mild. One of these children had received 40 c.c., and the other, 60 c.c. of serum. In the remaining six children the measles ran its usual course. In two there was a rise in temperature in the posteruptive stage, with evidence of pulmonary infiltration.

II. CONCENTRATED NORMAL SERUM IN PRE-ERUPTIVE MEASLES

Since convalescent serum is not always available, it was suggested that one could use serum obtained from adults who had had measles during their childhood. Adult serum has long been used in measles prophylaxis.

It has been estimated clinically that to obtain the same prophylactic results it is necessary to use three to four times as much adult serum as convalescent serum. Since we found that 40 c.c. to 50 c.c. of convalescent serum is necessary for modification of measles after clinical symptoms have appeared, it would seem necessary to give 150 c.c. to 200 c.c. of adult serum. Therefore, a method to concentrate such adult serum

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The authors had the cooperation of Dr. William Thalhimer, director of the Manhattan Convalescent Serum Laboratory.

Aided by grants from the New York, Friedsam and Nathan Hofheimer foundations.

would facilitate administration. Dr. Thalhimer,[5] employing a method he has described, concentrated adult serum for us, to one-third to one-quarter of the original volume.

The method for concentration can be described briefly as follows: Sterile serum is put into a sterile cellophane bag. The bag is suspended in front of an electric fan in a room or in a mechanical refrigerator. Moisture evaporates at the rate of from 20 c.c. to 25 c.c. an hour. The serum can be concentrated to any desired degree up to dryness. During evaporation the serum is kept at a temperature of 17° C. The serum so concentrated is quite viscous but can be drawn through a large bore needle for subcutaneous or intravenous injection.

The serum was prepared separately for the four different blood types. Each lot of serum was pooled from thirty-five to forty donors. It has been found recently that it is unnecessary to use typed serum if the concentrated serum is prepared from a large number of donors of the various blood types.

Twelve children admitted to the Willard Parker Hospital in the pre-eruptive stage of measles were given varying amounts of this concentrated serum intravenously. At the time of the injection definite Koplik's spots were present in all the patients; none of the children had previously received any measles convalescent serum.

After the blood type of the child was determined, concentrated serum of the same group was administered. The serum was concentrated to from one-third to one-quarter of its original volume. Three children were given 30 c.c.; two were given 50 c.c.; and seven were given from 60 to 70 c.c.

There was no modification of the measles in eleven of the twelve children. In one patient a sparse rash appeared four and one-half days after the administration of the serum. Eleven patients had unmodified measles; in two the rash appeared one day after serum administration, in four after two days, and in five after three or more days.

There was an untoward reaction within one hour after administration in three of the children. This reaction was characterized by fever and a mild chill. One of the children had a typical serum sickness.

COMMENTS

As was previously shown, adequate amounts of measles convalescent serum given intravenously during the pre-eruptive stage of measles modify the course of the disease in most instances. It is generally stated that specific therapy is of little avail in virus diseases once active symptoms have appeared. This dictum may not apply to measles.

However, once a rash appeared, we were unable to affect the clinical course of the measles even when using large amounts of serum. Perhaps if we had given larger amounts, some modification would have been obtained.

We offer no explanation as to why concentrated serum given to children in the pre-eruptive stage of measles apparently had no effect on the subsequent course. Such concentrated serum is potent in the prophylaxis of measles.

It is possible that the protective antibody in adult serum may be attenuated during the process of concentration for the following reasons:

1. The concentration of the serum at a temperature of 17° C. may not be optimum.
2. By concentrating the serum, its salt concentration is changed.

SUMMARY AND CONCLUSION

The intravenous injection of adequate amounts (40 to 50 c.c.) of convalescent serum, if given in the pre-eruptive stage of measles, modifies the course of the measles in most cases.

The intravenous injection of 40 to 105 c.c. of convalescent serum in the eruptive stage had little effect on the course of the measles. Exceptionally, when given at the very beginning of the eruption, the convalescent serum may cause some modification.

The intravenous injection of 30 to 70 c.c. of normal adult serum concentrated to from one-third to one-quarter of its volume had no effect on the subsequent course of the measles in twelve children.

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DIPHTHERIA AND CHEMOTHERAPY

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WITHIN the past year two articles[1, 2] have appeared in the pediatric literature indicating that the sulfonamide drugs may prove satisfactory in the treatment of diphtheria. The recent article by Abelson and Leichenger[3] is, however, a more convincing argument against the efficacy of this treatment than the others are for it. The question is of more than academic interest. In the past fifteen or twenty years there has been a rapid fall in the incidence of diphtheria, but the decline apparently has reached a standstill. The lack of diphtheria consciousness, the recent graduates' inexperience with the disease, and adult cases of diphtheria in a population where the young are immunized will explain this status quo above the desired irreducible minimum. To add to these sources of errors a false security in chemotherapy will be only one more reason for diphtheria to continue taking its toll.

Table I

ANIMAL	WEIGHT (GM.)	THERAPY	KLEBS-LÖFFLER BACILLUS CULTURE	SCHICK TEST
1	191	Antitoxin	Negative	Negative
2	242	5 c.c. human blood	2+	Negative
3	230	Sulfanilamide	4+	4+
4	231	Sulfapyridine	4+	4+
5	232	Sulfathiazole	4+	4+
6	174	None	4+	4+

In order to get further information on the effect of the sulfonamides on the Klebs-Löffler bacillus, a simple experiment was conducted. The technical part of the work was done by Dr. Helen Hardenbergh and Miss Esther Larson at Children's Hospital. The virulence test is a well-known procedure and was used as the basis for the experiment. In addition, the Schick test was done on the guinea pigs. Six guinea pigs weighing from 170 to 240 Gm. were used (Table I). One guinea pig was given a prophylactic dose of diphtheria antitoxin; a second was given 5 c.c. of human blood from a Schick-negative donor. To each of three pigs was administered one of the sulfonamide drugs—sulfanilamide, 0.8 per cent solution, sulfapyridine and sulfathiazole, 0.5 per cent solution, in the dosage of 0.15 Gm. per kilogram of body weight in twenty-four hours. The sixth pig was the untreated control. The drug was given hypodermically in divided doses at eight hourly intervals. The administration was started forty-eight hours before and continued for seventy-two

From Children's Hospital, San Francisco.

hours after the injection of the culture. A pure culture of Klebs-Löffler bacilli was obtained from Miss Bernice Eddie of the University of California. The Schick material used was Cutter's laboratory standard ready diluted Schick test. One-tenth cubic centimeter of a uniform heavy suspension of the culture was injected intradermally into a shaved area of skin on the lateral aspect of the abdomen of each guinea pig, and 0.1 c.c. of Schick material was injected on a similar area on the opposite side of each animal. The three animals on chemotherapy and the control animal had indistinguishable reactions. The virulence test became red and then proceeded through a stage of vesicle formation and necrosis which, at the end of five days, was a black scab about 1 cm. in diameter, with a desquamating area around it. The Schick test at the end of seventy-two hours showed beginning necrosis at the center. The animal given antitoxin showed no reaction at the site of either injection. The one receiving human blood had a negative Schick test and a modified virulence reaction with less necrosis and no desquamation around it. Although the experiment is not comparable to the treatment of diphtheria, it tends to confirm the clinical observations of Abelson and Leichenger. There is no evidence that the sulfonamides inhibit effectively the growth of the diphtheria bacillus or that they have any neutralizing effect on the toxin.

Even if one of these drugs were effective in inhibiting the growth of the Klebs-Löffler bacillus, chemotherapy would still not be the therapy of choice. Diphtheria kills by a highly virulent toxin alone. The organism has no invasive power; therefore, the disease is particularly suitable for antitoxin therapy. The sulfonamides, which act by inhibiting the growth of the organism and, consequently, the production of toxin, require a certain time limit for effectiveness. When the rate of progress of a disease is relatively slow, delay is of no particular consequence, for a lapse of twenty-four or even forty-eight hours does not materially alter the outcome of the disease. In those diseases, however, where the toxic component plays a major role and sometimes kills in minutes or hours rather than days, chemotherapy is not the therapy of first choice. In these diseases an antitoxin for immediate neutralization of the toxin is the logical treatment. In diphtheria, antitoxin alone is adequate; in other diseases, notably the fulminant cases of meningococcemia, a judicious combination of the two agents—antitoxin for immediate neutralization of the toxin and the sulfonamide drug for continued inhibition of the growth of the organism—is the therapeutic procedure preferable to the use of either agent alone.

The specificity and the therapeutic results of diphtheria antitoxin have been so remarkable that no patient with diphtheria should be deprived of antitoxin except under very unusual circumstances. A condition of exquisite horse serum sensitiveness would seem to be the only situation in

which other therapy might have to be considered. Mild degrees of sensitiveness do not preclude the use of commercial antitoxin. The present product is concentrated, thereby not only eliminating nonessential proteins, but also permitting the administration of a large dose in terms of units via a small volume of serum. If the intravenous route appears too hazardous, the serum is readily absorbed after intramuscular administration. It may be given in repeated small doses over a period of several hours, dosage being started with minimum safe amounts, thereby eliminating the danger of a sudden, overwhelming reaction. Only that patient who is so sensitive to horse serum that he cannot be given the antitoxin, even with these precautions, is a candidate for another type of therapy.

I have looked for such a patient for years in vain, because I wanted to treat him with human immune serum or blood. My curiosity on this subject was aroused several years ago when I observed that a Schick test could be readily neutralized by small amounts of serum or blood from Schick-negative persons.[4] This subject has been studied more elaborately recently.[5] The observation led to further studies on antitoxin content of human blood.[6] Anyone who pursues such study will reach the conclusion that some persons, like some animals, are very good antitoxin producers, having 30 or 50 units per cubic centimeter even after toxoid administration. In our study, not infrequently such a finding called forth the remark, "He could sell his blood for antitoxin." From what we know of immune blood in general and about antitoxin in particular, it would seem logical to treat the person hypersensitive to horse serum with human blood or serum. A serum with such a low antitoxin value should be administered in large doses, 200 to 300 c.c. or more intravenously. But even if the units of antitoxin are far below the recommended dosage, there is probably enough antitoxin in the blood temporarily to protect undamaged tissue and neutralize some of the free toxin, thus giving the patient a chance to mobilize his own immunity defense forces. Except in late or severe cases the patient should have a fair chance to survive.

The ideal donor for such blood or serum would be an individual whose antitoxin content was known to be high. Since this information is not generally available or readily and quickly determined, other sources of unknown value would usually have to be relied upon. Pooled adult blood would probably be of some value; a known Schick-negative person might be more valuable; and a known negative who had been given a dose of toxoid twelve to twenty-four hours before the blood was taken would be still better. (It has been amply demonstrated that there is no "negative phase" after toxoid administration.) Dry or bottled serum would be the most readily available for immediate use. This could then be followed up in twelve to twenty-four hours with a transfusion from

a known Schick-negative or a hyperimmunized person. In the experiment reported, 5 c.c. of human blood resulted in a negative Schick test and a modified virulence test in the guinea pig. The antitoxin content of the blood at the time used was not known, but when tested in the past it had been in the zone of from 0.5 to 5 units per cubic centimeter.[6] The injection resulted in only partial protection, and even this method of therapy, therefore, cannot be viewed with much equanimity. Since human serum stations have been established, it might be feasible to have some dry hyperimmune human serum of known diphtheria antitoxin content available for a rare emergency.

In conclusion, it may be said that the best evidence available indicates that chemotherapy has no effect on the diphtheria bacillus and should not be used as a blanket therapy to cover the treatment of all sore throats, including diphtheria. To reduce diphtheria mortality, the doctors must continue to extend prevention procedure and also learn to recognize and treat early with antitoxin the cases of the disease that occur. Even relatively sensitive patients can usually be treated by the careful administration of commercial antitoxin. A suggestion is made that, should a rare case of diphtheria occur in a person exquisitely sensitive to horse serum, human serum of high antitoxin content might furnish enough antitoxin to protect and partially neutralize the toxin, thereby giving the patient a chance to mobilize his own protective forces to conquer the disease.

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A STUDY OF THE RELATIONSHIP BETWEEN FETAL POSITION AND CERTAIN CONGENITAL DEFORMITIES

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UTERINE pressure occupies a prominent place in medical literature among the suggested causes of various congenital deformities. Few papers on the subject neglect to mention it. On the other hand, attempts at proof of the validity of the suggestion are rare, and when offered, the evidence is limited to that particular deformity or region which interests the author. Although few in number, these papers have demonstrated clearly that uterine pressure can affect various parts. It is assumed in the reports that fetal posture plays a role in the production of such

Fig. 1.—X-ray showing the marked curvature of the femurs and the laterally dislocated hips.

pressure, but despite this assumption, the position of the fetus seems never to have been taken into account. This paper has been written in an attempt to further the explanation of the mechanism involved by regarding the attitude of the entire fetus and to suggest a simple method for the determination of these attitudes. It is felt that not only may the cause of some deformities be demonstrated, but that by adding this maneuver to the routine examination of newborn infants, certain obscure deformities not apparent on the ordinary inspection may be detected. This early detection has prognostic significance and may have preventive value.

From the Department of Pediatrics, School of Medicine, University of Pennsylvania, and the Children's Hospital of Philadelphia.

Our interest in the subject was aroused by a male infant born with marked lateral bowing of both femurs (Fig. 1). His general physical condition was excellent although his mother was receiving treatment for syphilis. The baby's serology was negative, but on x-ray examination

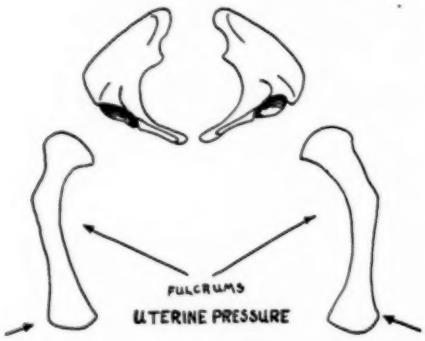

Fig. 2.—Diagram of the forces producing the curvature of the femurs, as seen from below.

Fig. 3.

Fig. 4.

Fig. 3.—"Position of comfort." With the feet fitted into the curvatures of the thighs and held there with tape, the infant immediately goes to sleep.

Fig. 4.—On release from the cramped position, the infant stretches his legs apprehensively and begins to cry.

there were areas of rarefaction visible in the shafts of the long bones which seemed attributable to syphilis. However, syphilis did not explain the anatomic aberrations, and no other explanation, either pathologic or embryologic, could be advanced for them; it was decided, therefore, to

look to the baby himself for the explanation. It seemed that the femoral bowing could have been produced in a bone softened by syphilis by a force on the knees directed centrally, or one at the apices of the curves directed laterally (Fig. 2). In either case a counterforce would be implied. If pressure from the wall of the uterus were assumed to be the mesially directed force, the counterforce might be a laterally directed fulcrum. To find such a fulcrum, we folded the infant so that each foot opposed the apex of the lateral curvature of the other thigh. This drew his legs up tailor-fashion so that each leg met the opposite femur at a right angle (Fig. 3).

To our surprise, the baby seemed to enjoy this position. Instead of objecting to being folded up, he preferred it, and he screamed when he was relaxed from the posture (Fig. 4). The crying could be stopped at any time by assisting the infant into the cramped position which for him was what we have come to call "the position of comfort." The complete contentment in an attitude which for another baby would be uncomfortable, if not impossible, seemed evidence to the fact that he had become accustomed to the posture before birth.

Further evidence lay in the fact that x-ray examination showed laterally dislocated hips and very shallow acetabula. Obviously, lateral dislocation can be caused only by a laterally directed force on the femurs. Such a force would be caused by the described intrauterine position producing a reversal of the normal pull of the femoral head toward the sockets and would result in a delayed ossification of the acetabula. Thus the shallow acetabula give corroborative evidence that the fetal position was responsible for the deformities of this infant.

With this deduction, we began determining the "position of comfort" of all newborn infants and soon learned that the positions occasionally included abnormal postures with no resulting deformity or with minor ones (Figs. 5 and 6), but that reconstruction of the position in infants with one or with no obvious deformity frequently led to the finding of unsuspected abnormalities.

Applying this theory as an explanation for a variety of orthopedic conditions, we first considered congenital dislocation of the hip. Since pressure is essential for the conversion of the cartilaginous acetabulum and femoral head into bone, any factor reducing the force of the head into the socket will diminish the rate of ossification accordingly. Even in the normal fetal position the thigh is so flexed by the uterus that it is not possible for the muscles attaching the thigh to the body to exert a force of great degree into the hip socket, as they do in any other position (Fig. 7). Indeed, the component of their greatest force is directed away from the acetabulum and the responsibility for maintenance of the close relationship of femoral head to acetabulum lies on the joint capsule and the small surrounding muscles. With only this

small support about the joint, it was deduced that congenital dislocation of the hip might result from two different sets of abnormal circumstances: first, in the presence of pressure besides the normal muscle pull such as might be supplied by the uterine wall on the knee; and second, in

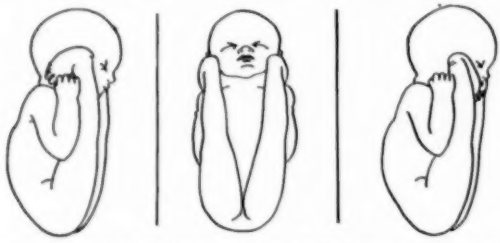

Fig. 5.—"Positions of comfort." (From Holt and McIntosh, D. Appleton-Century Co., p. 88.)

Fig. 6.—"Position of comfort." No deformity was present.

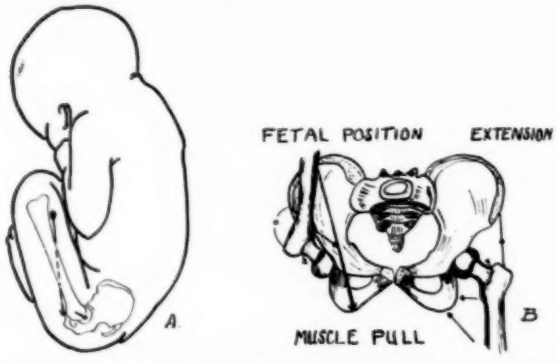

Fig. 7.—*A*, Diagram of the components of the forces exerted around the hip joint in the fetal position. The greater component is in a direction away from the socket. *B*, Diagram of the muscle pull, represented by arrows, in the fetal position and in extension.

the case of relaxation of the capsule (Figs. 8 and 9). When the factor is uterine pressure alone, i.e., without capsular relaxation, it is to be expected that the dislocation would be complete when it occurs, as it takes

place suddenly when the strained capsule gives way (Fig. 10). In this case ossification of the socket might have proceeded until the last, and therefore a good acetabulum could exist. This appears to be the case in two infants of our series. A great number, however, have evidence of relaxation of the capsule. This is demonstrated, first, by x-ray showing normal relationship between pelvis and femur, the only demonstrable pathologic finding being a lack of ossification of the socket and late appearance of the femoral epiphysis, while elsewhere ossification is normal, and, second, by the finding of capsular relaxations in the postpartum period.

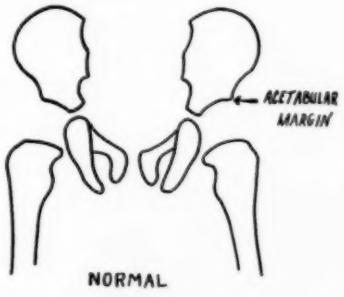

Fig. 8.

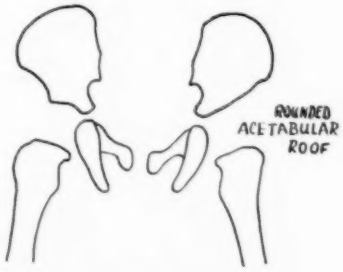

Fig. 9.

Fig. 8.—The acetabulum on each side is sharply outlined and its outer margin is angulated. The slant of the acetabular roof seems to be unimportant if this angulation exists.

Fig. 9.—This is the usual picture of congenital dislocation of the hip in the first two months of life. The acetabulum on the affected side has not yet ossified, as evidenced by the lack of angulation of the acetabular margin, and the femur and pelvis are still in normal relationship.

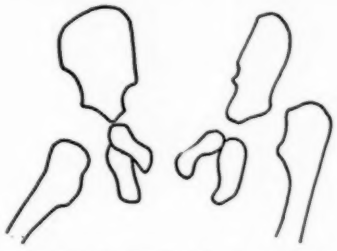

Fig. 10.—The rare type of congenital dislocation of the hip in which there is a true dislocation at birth. Note that the acetabulum may be fairly well formed.

It was suggested to us by Dr. Pendleton Tompkins in a personal communication that ligamentous structures in the fetus may be relaxed by the relaxing hormone of the mother. This suggestion would seem to suit the circumstances satisfactorily as the relaxation persists after birth for a length of time comparable to the duration of such other hormonal effects as vaginal discharge and breast enlargement, and it might account for the sex linkage of congenital dislocation of the hip which, in the form of delayed acetabular ossification, occurs so pre-

dominantly in the female. Further defense of the concept cannot be attempted until other studies are completed. However, it might be

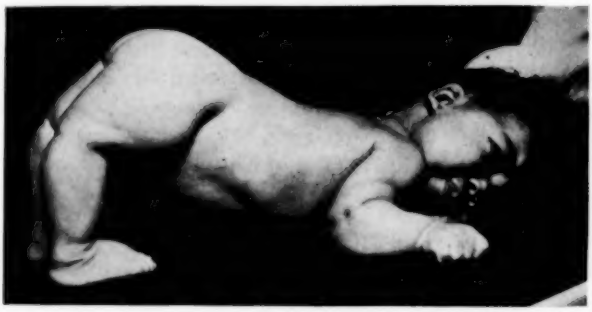

Fig. 11.—This photograph shows the infant in Fig. 21 as she returned to the hospital three months after discharge from the maternity nursery. Note the loss of elasticity most easily observed in her knees.

Fig. 12.—The same infant after an injection of estrogen. Because of the return of elasticity, she is unable to maintain the posture shown in Fig. 11.

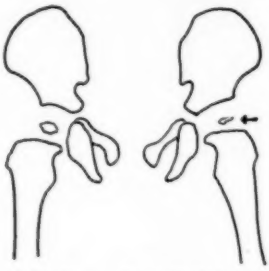

Fig. 13.—The femoral epiphysis on the affected side is small and irregular as compared to that of the normal side. This finding is commonly found in combination with the delayed ossification of the acetabulum, but may exist alone, as in this case. The space for the femoral head is narrow. Although the head itself is not visible, it can be assumed to be compressed. This child has the described clinical signs of early congenital dislocation of the hip.

mentioned here that we have had some success in restoring the relaxation of one infant who had lost her post-partum pliancy (Figs. 11 and 12) by injecting estrogen. Although our method was empirical, good

relaxation in guinea pigs has since been reported by Haterius,[1] using a similar method. Whatever the cause, it seems clear that relaxation exists to a mild degree in most infants and to a marked degree in many. In the presence of great relaxation, the fetal position may produce delayed

Fig. 14.—Limitation of abduction, the most commonly occurring sign in congenital dislocation of the hip. Note the prominence caused at the inguinal line by the adductor spasm on attempted passive abduction.

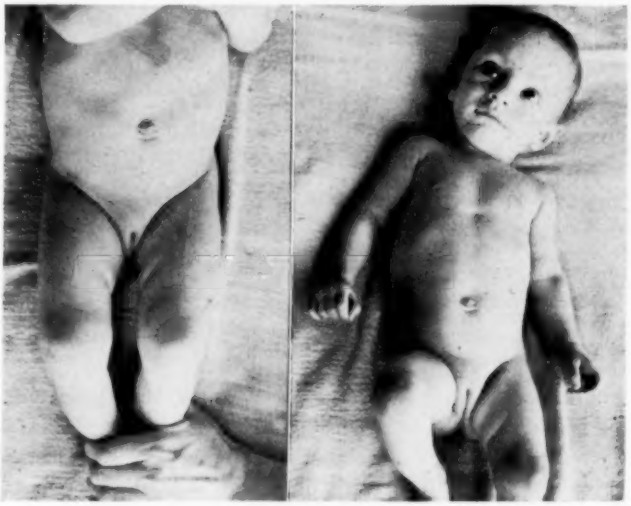

Fig. 15. Fig. 16.

Fig. 15.—Asymmetry of the inguinal folds. Note the angulation of the line on the affected side and partial concealment of the vulva in the fat of that thigh.

Fig. 16.—The affected leg is held quiet, in partial flexion The other leg is moved freely. This infant had a deviation of the jaw, and even at 5 months of age, when this photograph was taken, still tilted her head to the left.

ossification of either the acetabulum or the femoral head or both, as the one is subjected to pressure only by the other; only the severe degrees, however, are of clinical importance.

When the delay in ossification is present in the femoral head only, roentgenograms of the condition resemble those seen in Perthes' disease. (Fig. 13). The cartilaginous state of the femoral head subjects it to pressure malformations which would be resisted by the structure if normally ossified.

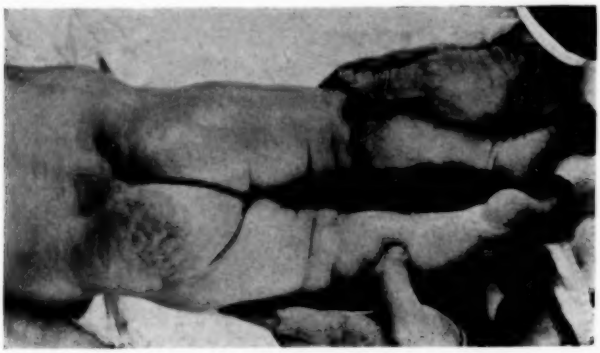

Fig. 17.—Asymmetry of the gluteal folds. The higher fold is on the affected side.

Fig. 18.—"Position of comfort." The very common finding of relaxation of the knee capsule, with anterior "dislocation."

It is of interest that the three types of hip difficulty have one predominant sign when the initial relaxation of the newborn infant has disappeared. That sign is limitation of abduction (Fig. 14) and is due to the splinting of the unstabilized femoral head by its surrounding muscles.[2] At about six weeks a difference in the inguinal (Figs. 15 and 16) and gluteal folds (Fig. 17) develops, which depends upon the ascent from the socket in the one type and upon the deformation of the femoral head in the other. In the rare third type, in which true dislocation exists at birth, the femoral head can be palpated in its dislocation and the folds are asymmetrical from birth.

The hip is the most commonly affected joint because only in it does the fetal position reverse the normal direction of force. "Dislocation"

of the knee, the next most common dislocation, occurs clinically only one-ninetieth as often. However, we have found "dislocation" of the knee, both of the anterior (Fig. 18) and the posterior or back knee

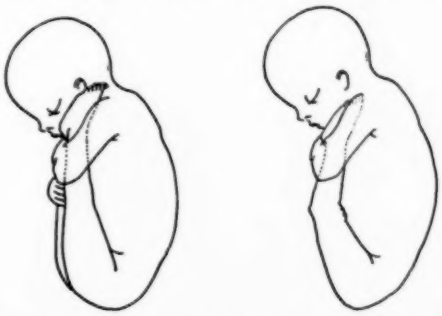

Fig. 19.—"Positions of comfort." These sketches represent the steps in the production of hyperextension of the knee. (From Holt and McIntosh, D. Appleton-Century Co., p. 88.)

Fig. 20.—"Position of comfort," with one knee in hyperextension.

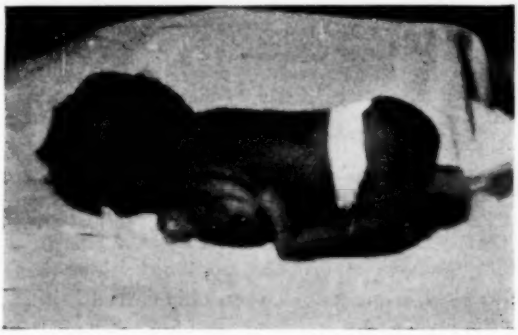

Fig. 21.—"Position of comfort," with both knees in posterior dislocation. The elbows and hips are dislocated as illustrated in Fig. 22.

varieties (Figs. 19 and 20), to be not infrequent in the newborn infant, and we have found examples of the even more rare dislocations of the shoulders, elbows, and wrists. Three of the infants with back knee

recovered spontaneously within a week as the infants lost their initial pliancy. Three others had back knee of severe degree as part of a relaxation and pressure phenomenon (Fig. 21) which caused dislocated hips in all of them, as well as elbow dislocation in two (Fig. 22) and clubbed feet in the third.

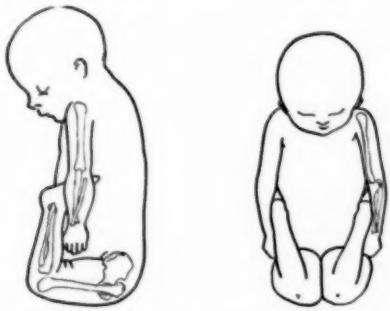

Fig. 22.—"Position of comfort." This infant has passed through the hyperextension mechanism of the preceding sketch. With her knees completely dislocated, uterine pressure exerted on them dislocated her hips posteriorly and inferiorly. Her elbows were dislocated by uterine pressure which utilized the feet as fulcrums.

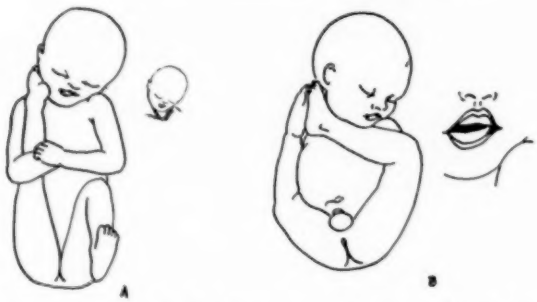

Fig. 23.—"Positions of comfort" demonstrating the production of deviation of the jaw. The infant in *A* had a torticollis and a mild talipes varus. The infant in *B* had limitation of flexion in the left knee and a shallow acetabulum on that side. Small sketches show details of pressure mechanism on the chin. (From Holt and McIntosh, D. Appleton-Century Co., p. 88.)

Several infants with signs of pressure on their mouths and jaws showed by their "positions of comfort" that one or both legs had been extended across the body, bringing a foot to one side of the head, and thereby forcing the head against the opposite shoulder (Figs. 23, 24, and 25). In this group is one case of torticollis caused in this manner, but most of the group have simply a deviation of the jaw. We have observed many of these and many more are reported in the literature. While this asymmetry itself is unimportant, the reconstruction of its etiological mechanism demonstrated the source of pressure on the clubfeet of three infants; it led us, in one case, to anticipate a delayed femoral epiphysis and to explain a knee defect, and in another instance to suspect and

diagnose a delayed acetabular ossification which would have proceeded to dislocation of hip.

Fig. 24.—"Position of comfort."

Fig. 25.—Mild talipes varus associated with deviation of the jaw and congenital dislocation of the hip.

In conclusion, we feel that it is important to determine the "position of comfort" as a routine part of the examination of newborn infants, both as a means of anticipation and prevention of bone and joint abnormalities and as an aid to the interpretation of existing deformities.

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PRIMARY ARTERITIS (PERIARTERITIS NODOSA) AMONG CHILDREN

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PERIARTERITIS nodosa was first described by Kussmaul and Maier in 1866. Since that time many cases have been reported and studied. In spite of careful clinical, bacteriologic, and especially pathologic studies, the cause of this disease is still unknown. It appears among both children and adults, the reported range of age extending from 3 months to 78 years. Numerous excellent clinical and pathologic studies on the subject have been made within the past few years, and the number of recognized cases has been increasing. Rothstein and Welt in 1933 found a total of 195 cases in which patients were of all ages. By 1938 the total number of cases had increased to 395 (collected by L. J. Boyd). Rothstein and Welt summarized all the cases reported in which children were affected and added two of their own, bringing the total number of such cases to twenty-three. Since their report we have found reports of nineteen other similar cases, and we wish to add two of our own, to bring the total to forty-four cases. It is of interest to note that from 1866 to 1932, inclusive, a period of sixty-seven years, twenty-three cases in which children were involved were reported. From 1933 to 1939, inclusive, a period of seven years, twenty-one more such cases were reported. The majority of these were reported in detail; in only one case (Spiegel's second case) was the information too scanty for the reader to be certain of the diagnosis.

DIAGNOSTIC CONSIDERATIONS

Diagnosis.—Because of the unknown causation and bizarre symptomatologic aspects of periarteritis nodosa, diagnosis of the condition is rather difficult and is made during the life of patients in only about 15 per cent of cases. Although the disease has no typical course, diagnosis is suggested by one or more of the following signs and symptoms: (1) a prolonged septic temperature which cannot be otherwise explained, (2) occurrence of symptoms in various parts of the body which can be related to arterial occlusion, such as regions of gangrene and ecchymosis as described by Barnard and Burbury, Vining, and Vránová, and (3) appearance of nodules under the skin, particularly in relation to the smaller arteries.

Differential Diagnosis.—Because of the general and nonspecific nature of the symptoms, the disease has been confused with numerous other

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conditions. The appearance of cutaneous hemorrhages in some cases suggested hemorrhagic purpura. The prolonged elevation of temperature and other considerations suggested typhoid fever, miliary tuberculosis, hepatic abscess, or meningitis. In still other cases the condition has been diagnosed as myositis, trichinosis, polyneuritis, or tumor of the brain. Kernohan and Woltman reported five cases in which microscopic changes were observed in the nervous system, and they also reported that 8 per cent or more of patients who have periarteritis nodosa have neurologic symptoms. The frequent occurrence of severe abdominal pain suggests the action of acute intra-abdominal disease. Periarteritis nodosa also must be distinguished from rheumatic fever because pains in muscles or joints frequently occur when periarteritis is present. Some authors have suggested that periarteritis nodosa and rheumatic fever might in fact be the same disease, but such a suggestion has been fairly generally disproved. A common complication of periarteritis nodosa is nephritis, and the occurrence of such renal involvement should at least suggest the possibility of periarteritis nodosa.

CLINICAL OBSERVATIONS IN THE LITERATURE

In reviewing the clinical observations made in the forty-four reported cases (Table I), we found that evidences of infection (irregular fever and leucocytosis) were the most common. Irregular fever was definitely present in thirty-eight of the forty-four cases, and leucocytosis was recorded at some stage of the disease in twenty-eight cases. Leucocytosis may have been still more frequent than it appeared, since in some reports the leucocyte count was not mentioned. Abdominal pain (usually recurring and severe) and "rheumatic pains" (pains in the muscles or

TABLE I

SYMPTOMS OF PERIARTERITIS NODOSA AMONG CHILDREN: ANALYSIS OF FORTY-TWO CASES IN THE LITERATURE PLUS TWO ADDED BY THE AUTHORS

SYMPTOMS	NO. OF CASES	PER CENT
Fever (intermittent usually)	38	86
Leucocytosis	28	63
Abdominal pains	23	52
Rheumatic pains	22	50
Renal disease	18	40
General weakness	17	38
Convulsions	17	38
Tachycardia	15	34
Anemia	15	34
Purpuric rash	12	27
Other rashes; e.g., urticaria	9	20
Hypertension	9	20
Tonsillitis or sore throat	8	18
Headaches	7	16
Intestinal hemorrhage	4	9
Peripheral gangrene	4	9
Meningitis signs	3	7
Palpable nodules	2	4.5

the joints) were also rather frequent, the former occurring in twenty-three cases and the latter in twenty-two. Evidence of renal disease (albuminuria, hematuria, and the like) was recorded in eighteen cases. It has been pointed out by other writers that renal disease is a definite and important part of periarteritis nodosa. In seventeen cases generalized weakness was specifically described, and this symptom undoubtedly occurred in others. Generalized convulsions also occurred in seventeen cases. Tachycardia, anemia, and purpuric rashes each occurred in approximately a third of the cases. Urticaria or other unusual cutaneous manifestations appeared in nine cases, as did hypertension. The blood pressure, however, was not recorded in many of the cases, and hypertension may have been more frequent than was reported. Persistent headache, intestinal hemorrhage, and signs of meningeal irritation occurred in a few cases. Of particular interest is the fact that peripheral gangrene was reported in four cases. At least one of the patients so affected recovered, and there remained several scarred regions in which gangrene of the skin had occurred.[21] It is also to be noted that, of this whole series of forty-four cases, palpable nodules were found in the skin in only two.

PATHOLOGIC ANATOMIC ASPECTS

No attempt will be made to make a complete review of the pathologic observations in the reported cases. The disease is essentially a disease of the smaller arteries, and lesions may occur in any organ and may involve a small or large part of that organ. It is generally agreed that the renal, coronary, mesenteric, and hepatic arteries are the vessels most frequently involved. The nervous system is probably more often affected than is supposed (Kernohan and Woltman). Gross lesions in the vessels often are not prominent, although nodules, aneurysms, or thrombosis may be encountered. More frequently, complications of the disease, such as hemorrhages and infarcts, are the only grossly visible changes.

Histologically, a wide variety of lesions have been described, probably because the inflammatory process has been studied by different investigators in various stages of its development. Such a variety of lesions may also indicate that various etiological agents are involved. Arkin has divided the disease process into four stages on the basis of the histologic appearance of the lesions. The first stage is dominated by changes such as necrosis of the inner media in arterioles and in the outer media in larger arteries. Edema and fibrinous exudate are also present. In the second stage exudative inflammation is predominant, and the media and the adventitia are the seat of massive accumulations of polymorphonuclear cells, eosinophilic leucocytes, lymphocytes, and plasma cells. Intimal connective tissue proliferation and complications

such as formation of aneurysm, thrombosis, and hemorrhage occur toward the end of this stage. In the third stage the regenerative and proliferative processes are predominant. Organization of thrombi and formation of granulation tissue take place. The final stage is characterized by formation of scar tissue and healing.

Death generally is the result of complications of the disease, such as thrombosis and hemorrhage. Infarction and necrosis which result may be rapidly disastrous when they occur in the bowel, heart, or brain. Renal insufficiency and pneumonia are complications which also frequently result in a fatal outcome.

CASE REPORTS

CASE 1.—A boy, 14½ years old, was admitted to the clinic on Jan. 20, 1938, and was dismissed on Feb. 11, 1938. His chief complaint was fever for which no cause had been found and which had been present for about two weeks. Headache accompanied the elevation of temperature, which had been as high as 105.5° F. (41° C.) at one time, but which had been lower than this most of the time. Coincidentally, the pulse varied in rate from 70 to 120 beats per minute. The patient had been constipated during these two weeks and had experienced one attack of pain which had lasted from three to four minutes in the right lumbar region. He also stated that during the previous two years he had had occasional attacks of pain in the same region. The boy had had mumps, whooping cough, and chicken pox but no other diseases. The family history was not pertinent to his condition. He was thought to have had contact with a person in the active stage of pulmonary tuberculosis in November, 1937.

The patient's blood pressure was 120 systolic, and 60 diastolic, expressed in millimeters of mercury, pulse rate 80 beats per minute, and temperature 100° F. (37.7° C.) by mouth. The patient was well developed although somewhat undernourished. Results of examination of the abdomen were entirely negative. On examination of the eyegrounds the fundi were found to be essentially normal, but there were some yellowish spots around the left fovea which were possibly seats of degeneration. The significance of these was not definite.

The patient was admitted to the hospital. He remained there for three weeks. During this time his temperature was "septic" in type. It varied from 98° to 103° F. (36.6° to 39.4° C.). It remained above normal each day for eighteen days. The temperature finally receded to normal and remained so for four days, and the patient was dismissed from the hospital. Results of urinalysis were entirely negative on three different occasions. When the patient was first admitted to the hospital, the hemoglobin content was 8.1 Gm. per 100 c.c. of whole blood, erythrocytes numbered 3,740,000, and the leucocytes numbered 7,200 per cubic millimeter. There were 18 per cent lymphocytes, 6 per cent monocytes, 73.5 per cent neutrophiles, 1.5 per cent eosinophiles, and 1 per cent basophiles in the differential count. (Ten days later the hemoglobin content was 8.9 Gm. per 100 c.c. of blood, erythrocytes numbered 4,820,000, and leucocytes numbered 6,500 per cubic millimeter.) Results of the flocculation test for syphilis were negative. A blood smear revealed hyperchromic microcytic anemia, toxic polymorphonuclear cells, and a moderate shift to the left. Results of a roentgenogram of the thorax were entirely negative as were results of roentgenograms of the paranasal sinuses, kidneys, and bladder. It was suspected that the patient might have tuberculosis of the hip, but results of roentgenographic examination were entirely negative. One roentgenogram of the thorax

revealed a Ghon complex at the right base, but otherwise nothing unusual. A blood culture was completely negative. Results of examination of the urine for *Mycobacterium tuberculosis* were negative on three different occasions. Results of the blood agglutination test revealed no evidence of brucellosis, typhoid fever, or paratyphoid fever. Reaction to the tuberculin test, performed with first strength purified protein derivative, was faintly positive; reaction to this test when it was performed with second strength purified protein derivative was strikingly positive within twenty-four hours. Shortly before the patient left the hospital, the value for hemoglobin was 11.9 Gm. per 100 c.c. of whole blood; erythrocytes numbered 4,960,000; and leucocytes numbered 6,200 per cubic millimeter. The patient appeared to be in good health. He received two transfusions of blood during his stay in the hospital.

He was again examined six months later. He stated that during this interval he had experienced episodes of a rapid pulse with chills and sometimes occasional pain in the left portion of the thorax. He had remained in bed during these episodes. When he was lying down, his pulse varied from 76 to 80 beats per minute. When he was standing, it became approximately 130 beats per minute. The heart sounds were not unusual. There were no murmurs, and the patient appeared generally to be well.

The patient was not seen again at the clinic, but his mother reported that in March, 1939 he again began to suffer from low-grade fever with severe headaches, sore throat, pains in the thorax and over the body generally. A large carbuncle had developed on the back of his neck, and his urine became bloody. Examination by his local physician revealed injection of the throat and edema of the ankles. He had albuminuria, grade 4+. The nonprotein nitrogen content of the blood was 140 mg. per 100 c.c.; the urea nitrogen, 64 mg. per 100 c.c.; and the creatinine, 3 mg. per 100 c.c. Health of the patient declined gradually, and he lapsed into uremic coma. He died at home on April 13, 1939.

At necropsy the peritoneal cavity contained 500 c.c. of clear yellow fluid. The liver extended 5.0 cm. below the xiphoid process, but in the midclavicular line it was even with the right costal margin. The mesenteric lymph nodes were much enlarged, and on cut section they appeared to be edematous.

There were about 50 c.c. of a light brown, clear fluid in each pleural cavity. The pericardium measured 13 cm. transversely, and there were 50 c.c. of clear yellow fluid in the pericardial sac.

The heart weighed 400 Gm., as compared to the normal weight of 200.6 Gm., suggested by Coppoletta and Wolbach, and it was pale reddish brown. The left ventricle was dilated to grade 2+.

All lobes of both lungs were very edematous and congested. The hilar, mediastinal, and tracheal lymph nodes were enlarged, and on section portions of caseation were seen. The spleen and liver weighed approximately twice the suggested normal weight. The kidneys appeared to be grossly typical of subacute glomerulonephritis.

Histologically, the most important lesions were present in the kidneys, heart, lymph nodes, and intestine. Most of the small arteries of the kidney were the seat of acute and subacute suppurative inflammation (Fig. 1). The adventitia of these vessels especially was densely infiltrated by polymorphonuclear and mononuclear leucocytes and fibrin. The exudate extended beyond the adventitia into the surrounding renal parenchyma on the one hand and into the media on the other. The exudate was so dense that the adventitia was almost entirely replaced by it. Only a few swollen fragments of fibers which stained deeply with eosin could be seen between the cells of the exudate. Fibroblastic proliferation was also present in the exudate of some vessels and suggested that the inflammatory process had varied in duration.

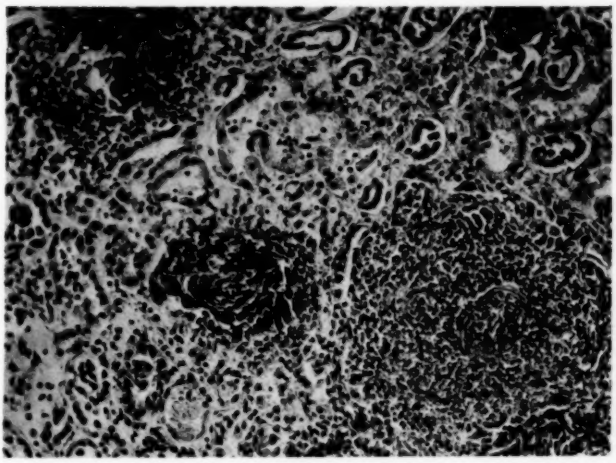

Fig. 1.—Subacute glomerulonephritis and periarteritis nodosa (Case 1); inflamed artery in upper left-hand corner (hematoxylin and eosin; ×130).

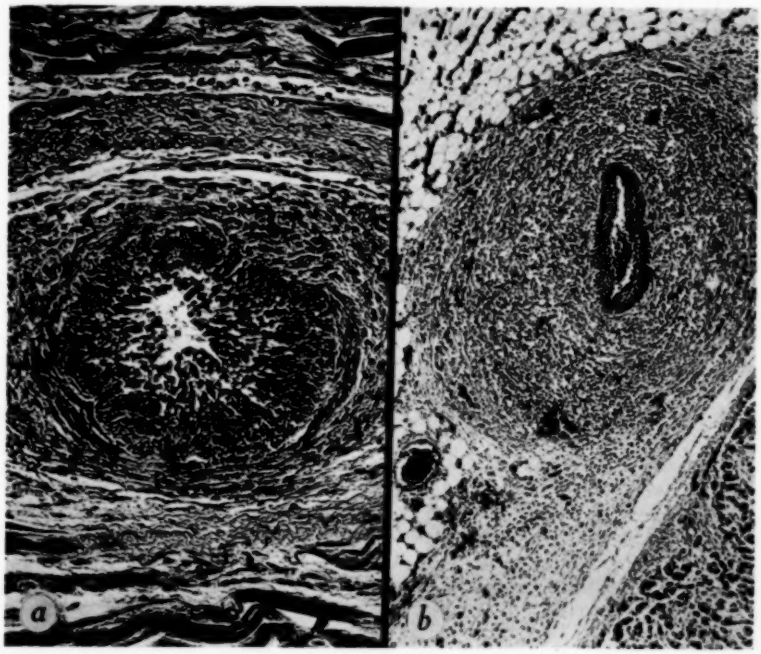

Fig. 2.—Periarteritis nodosa (Case 1); *a*, branch of coronary artery; necrosis of media with cellular infiltration of all coats and extension to surrounding connective tissue (hematoxylin and eosin; ×160); *b*, small artery of periadrenal connective tissue; cellular infiltration of entire wall with extension into surrounding fat (hematoxylin and eosin; ×50).

The muscle and elastic fibers of the media could not be recognized as such, since the entire media appeared as a band of swollen and fragmented collagen staining deeply with eosin. In most vessels the media also was infiltrated by polymorphonuclear and mononuclear leucocytes, but to a lesser extent than the adventitia. The only apparent change in the intima was slight proliferation of the endothelial cells, some of which were sloughing into the lumen. Thromboses or aneurysms were not found. In addition to the arterial lesions there was evidence of severe subacute glomerulonephritis.

A number of branches of the coronary arteries in the septum also were the seats of acute and subacute inflammations (Fig. 2*a*). The lesions were similar to those described as found in the arteries of the kidney. In the myocardium there were focal collections of polymorphonuclear cells. The only changes in the muscle fibers in these situations were loss of striations and pyknotic changes in the nuclei.

In the hilar, mediastinal, and mesenteric nodes active tuberculosis was present. The arterioles of some of the lymph follicles also were the seats of suppurative arteritis. In the submucosa of the small intestine many small arteries revealed acute inflammation and necrosis. Thrombosis had occurred in some of these vessels. There were severe edema and congestion of the submucosa with actual necrosis of the mucosa.

Arterial lesions similar to those already described were present in a few arteries in the liver, voluntary muscle, thymus body, and in the connective tissue around the adrenal bodies and around the prostate gland (Fig. 2*b*).

The following anatomic diagnoses were made: generalized primary arteritis (periarteritis nodosa), subacute glomerulonephritis with hypertrophy of kidneys, hypertrophy of the heart with dilatation of left ventricle grade 2, edema and congestion of lungs, and chronic tuberculosis of the hilar, mediastinal, and mesenteric lymph nodes.

CASE 2.—A girl, 3½ years old, was admitted to the clinic on Oct. 27, 1939, because of weakness and abdominal pain. She apparently had been well until May, 1939, five months before her admission. At that time it had been noted that she exhibited unsteadiness in walking. At the same time her left arm was somewhat swollen and tense from the elbow to the wrist and was stiff and painful on movement. At that time, also, the parents had noticed that the child did not care to play with other children as she had previously. In September it had been noted by the patient's home physician that there were limited movement of the shoulder and elbow, brown pigmentation of the skin, and a small growth situated just above the knee. Results of roentgenograms of the left arm and shoulder at this time were negative. Two weeks before coming here, the patient had complained of pains in the abdomen and had vomited once. Her appetite became poor, and she lost weight steadily. She had vomited every day for a period of nine days before admission to the clinic.

On examination the child was thin and apparently chronically ill. She complained constantly of abdominal pain. Over the back and over the feet there were large regions in which loss of normal pigmentation of the skin was observed. Numerous small red blotches were observed on the palms of the hands. Several cervical lymph nodes were palpable, and two inguinal nodes could be felt readily. The heart appeared to be enlarged to the left on percussion. Palpation of the abdomen disclosed generalized tenderness more marked in the left upper quadrant. The edge of the liver was just palpable. The spleen could not be felt. It was found that the left forearm appeared to be more firm in consistency than the right, and the patient had difficulty in straightening out the elbow on the left.

On admission to the hospital on October 27, the child's temperature was 101° F. (38.3° C.) but decreased to 99° F. (37.2° C.) on the third day after admission and then rose rapidly on the fourth day. By the fifth day it had reached 106° F. (41.1° C.). The pulse rate on admission was 100 beats per minute, and the blood pressure was 100 systolic and 60 diastolic, expressed in millimeters of mercury. Results of urinalysis were entirely negative, and the urine was sterile on culture. There were 11,900 leucocytes per cubic millimeter of blood. Results of a roentgenogram of the thorax were negative. A roentgenogram of the arm showed some thickening of the epiphyseal line of the radius and ulna, and an irregularity in the contour of the first left metacarpal bone, with apparent cortical thinning. The serologic reactions were most contradictory. Reaction to the Kline test was plus or minus, reaction to the Kahn test was plus-minus, reaction to the Hinton test was negative, and the reaction to the Wassermann test was strongly positive, grade 2 to 3. During the last thirty-six hours of the child's stay in the hospital, additional intense abdominal pain developed. The abdomen became distended, and the patient rapidly began to exhibit the symptoms of peritonitis and collapse. She failed to respond to supportive measures and died, apparently from acute intoxication.

Emaciation had been present and was graded 2 on a basis of 1 to 4. The first metacarpophalangeal joint of the left hand appeared to be enlarged and swollen. The peritoneal cavity contained 400 c.c. of bloody fluid, and the omentum was adherent by a few fresh adhesions to some loops of small intestine. The intestines and vermiform appendix were covered by fibrinopurulent exudate. An encapsulated pocket containing approximately 10 c.c. of pus was situated posterior to the splenic flexure of the colon. The heart appeared grossly to be normal.

In the upper lobe of the left lung there was a region in which consistency was markedly increased and crepitation was decreased. On the cut surface, this region of increased consistency revealed gray streaking on a pink background. The region involved measured 6.0 cm. in diameter. Its appearance suggested the effects of organized pneumonia.

The stomach contained 75 c.c. of bloody mucus. The mucosa of the fundic portion was swollen, hemorrhagic, and ulcerated. The mucosa of the duodenum was covered by a shaggy, pseudomembranous exudate. From the jejunum to a region 4 cm. above the ileocecal valve, the small intestine was dark reddish brown. When this portion of the bowel was opened, the lumen contained blood and it was apparent that, except for a few small patches, the entire wall was affected by infarction and gangrene, with ulceration of the mucous membrane. In the cecum and also as far as the midportion of the ascending colon there were numerous, punched-out ulcers with indurated edges which measured from 0.5 to 1.5 cm. in diameter. There was a hemorrhagic infarct which measured 1 cm. in its greatest extent, situated in the right kidney. The other organs revealed no abnormalities. The brain was not examined.

Histologically, the epicardium contained focal collections of lymphocytes. The intima of some of the small arteries of the epicardium was greatly thickened by proliferation of loose connective tissue which compromised the lumen. In the media, portions of the elastic and muscular fibers had undergone fragmentation and necrosis, and the collagen fibers of the adventitia appeared to be swollen. They stained deeply with eosin. Lymphocytes were numerous in the adventitia and periarterial tissue (Fig. 3*a*). Typical Aschoff bodies were not seen, however. Similar but less striking changes were present in the arteries of both ventricles and the septum. In the myocardium were regions of degeneration and collections of lymphocytes and plasma cells. In other situations, there were small regions in which muscle cells were being replaced by fibrous connective tissue. In the mitral valve there was edema of the connective tissue, together with increased numbers of lymphocytes and plasma cells.

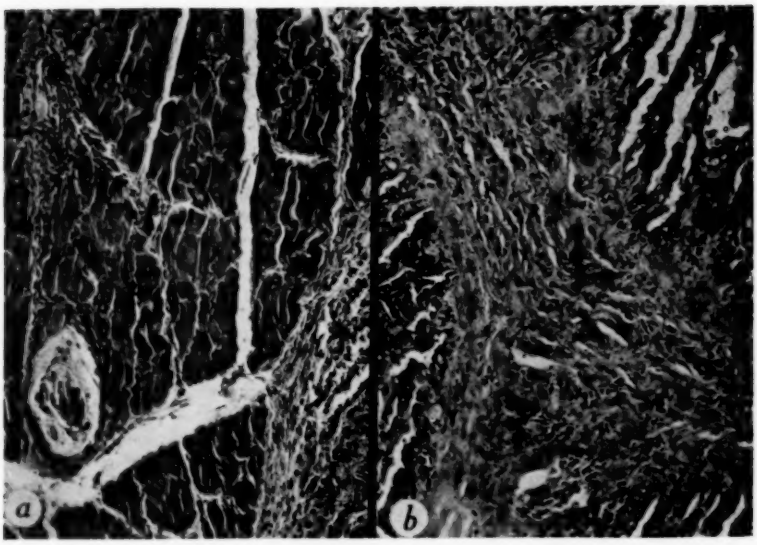

Fig. 3.—Inflammation of connective tissues (Case 2); *a*, heart: collections of lymphocytes and histocytes in septa of connective tissue; focal degeneration of myocardium (hematoxylin and eosin; ×110); *b*, upper lobe of left lung: increase of pulmonary connective tissue which appears swollen (fibrinoid degeneration?) (hematoxylin and eosin; ×115).

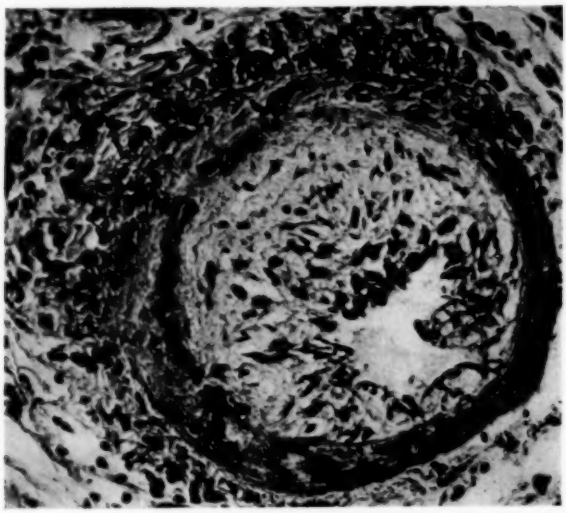

Fig. 4.—Periadrenal artery (Case 2): necrosis of media with cellular infiltration of adventitia and proliferation of intimal connective tissue (hematoxylin and eosin; ×300).

In histologic sections from the region of increased consistency in the upper lobe of the left lung there was massive thickening of the connective tissue septa. Throughout this fibrous connective tissue, but especially about the vessels and bronchi, the bundles of collagenous fibrils appeared swollen. They stained deeply with eosin. In some regions the collagen was fragmented as well as swollen, and there were accumulations of lymphocytes, plasma cells, and histocytes (Fig. 3*b*). These collections were strongly suggestive of Aschoff bodies. In the adventitia of the small arteries the collagen fibers were also swollen, and numerous lymphocytes were present. Many of the elastic and muscle fibers of the media had been undergoing necrosis and fragmentation. The intima of most of these vessels was greatly thickened by proliferation of loose connective tissue which compromised the lumen. Many of these vessels were occluded by organized thrombi.

The alveolar walls were thickened by proliferation of connective tissue, and many of the alveoli were filled with serous exudate which contained many large mononuclear cells. In sections from the other lobes of the lungs the arterioles were less severely affected and thickening of the connective tissue septa and alveolar walls was either absent or slight.

In histologic sections of the liver there was a small region of necrosis of hepatic cells with numerous hemorrhages. The periportal connective tissue was much increased in amount and revealed the same changes as those described in the lung. Focal collections of lymphocytes, fibroblasts, and large histocytes also were present. In the walls of the small arteries changes similar to those described in the lung were present. Other sections of the liver were essentially normal.

In many of the small arteries in the serosa of the stomach the same changes were present as those found in the vessels of the lung and liver. In the muscularis were foci of degenerative changes in the muscle fibers, as well as collections of lymphocytes and plasma cells. In the mucosa were regions of hemorrhage and necrosis. In the duodenum were similar lesions in the muscularis and mucosa, together with severe edema of the submucosa.

The smaller branches of the mesenteric artery were the seats of lesions similar to those already described. Many of the vessels had pronounced intimal thickening. The lumen of a large branch of this artery was narrowed by proliferation of loose connective tissue of the intima and was completely occluded by lodgment of a rather recently formed thrombus.

The lesions of the ileum varied in severity from small hemorrhages and ulcers of the mucosa to complete necrosis of the entire wall of the structure. In the cecum there were similar but smaller and more widely scattered lesions.

Arterial lesions similar to those already described were present in the heart, pectoral muscle, kidneys, thymus body, ovaries, uterus, and in the connective tissue around the adrenal body (Fig. 4).

In sections from the skin of the left forearm there was atrophy of the epidermis, and the collagenous fibers of the dermis were swollen and appeared to be edematous. The hair follicles and sebaceous glands also were atrophied. Exudative processes were not apparent.

In histologic sections of the first metacarpal bone, there was evidence of chronic periostitis.

The following anatomic diagnoses were made: Generalized primary arteritis (periarteritis nodosa), multiple acute infarcts of the gastrointestinal tract and kidneys, general peritonitis, fibrosis in the upper lobe of the left lung (fibrositis?), chronic focal infarction of the liver, emaciation, chronic focal myocarditis, and mitral valvulitis.

COMMENT

The two cases presented herein were dissimilar from the clinical viewpoint. The first patient (a boy 14½ years old) had an unexplained septic type of fever for a period of at least five weeks at the onset of the disease. He was well for a month when symptoms referable to the heart occurred. He apparently had attacks of tachycardia with chills, occasional pain in the region of the heart, and a sensation of "tightness" in the throat. Some months later nephritis developed and caused his death. In all, his illness lasted sixteen months.

The second patient was much younger (a girl 3½ years old). Her initial difficulty was pain with swelling in the left forearm as well as unsteadiness in walking. The swelling in the arm persisted, and stiffness of the elbow resulted; this may well have been caused by occlusive arterial disease. She remained reasonably well for five months; then, three weeks before her death, abdominal pain and vomiting occurred and persisted, with terminal signs of peritonitis.

From a histopathologic standpoint, the lesions in the two cases also were different and distinct. In Case 1 the lesions appeared as acute or subacute suppurative processes involving the walls of the vessels and extending well beyond the adventitia into the surrounding tissue. They were all in approximately the same stage of development, and alterative and exudative changes were predominant. In Case 2, however, most of the lesions appeared to be definitely regressing; the proliferative changes were predominant whereas exudative phenomena in the arteries were relatively slight. Other cases in which there was histologic evidence of healing in the lesions have been reported by Pickert-Menke, Spiro, Manges and Baehr, Arkin, and Cathala and Boegner. Another difference was the pronounced involvement (Case 2) of the fibrous connective tissues, especially in the lungs, heart, and skin. The character of the changes in the collagen fibers (fibrinoid degeneration) and the cellular proliferation was similar to that described as occurring in rheumatic fever.

A number of workers, notably Ophüls, Friedberg and Gross, Middleton and McCarter, and Neale and Whitfield, have stressed the close relationship between periarteritis nodosa and rheumatic fever. Friedberg and Gross, in particular, believed rheumatic fever to be a common cause of the vascular lesion termed "periarteritis nodosa."

Walter in 1921 reported histologic observations similar to those noted in our second case and stated that extension of the inflammation to the perivascular connective tissue led to the formation of inflammatory granulation tissue and a "cirrhosis-like" phenomenon. In Ophüls' and Mönckeberg's cases there was also involvement of the pulmonary vessels with marked extension of the subacute inflammation into the adjoining pulmonary tissue. In our case, however, it would seem that the fibrous

connective itself was the seat of the same type of inflammation as the arteries and that it was not merely secondarily involved. It is noteworthy that eosinophilic leucocytes were not present in significant numbers in either case.

Whether or not we encountered two different infectious agents in these cases is a point that is debatable and it cannot be decided definitely. It is apparent that the lesions represented different reactions, but whether these differences can be explained as being merely different stages of the same infectious process, or as indicating different immunologic responses, or as being evoked by different etiologic agents it is difficult to say. There was nothing in the histologic appearance of the arteries that pointed to a specific etiologic agent. Results of staining for *Mycobacterium tuberculosis* and other organisms were negative. It is noteworthy that in the first case the patient had suffered from renal insufficiency and hypertension (on the basis of the weight of the heart). It may be that the arterial changes were, in part, results of these two factors, since it is well known that necrotizing arteriolitis not infrequently occurs in hypertension associated with renal insufficiency (so-called malignant hypertension).

It is likewise noteworthy that macroscopic nodules and aneurysms were not present in either case and that in both instances formation of a correct diagnosis was possible only after study of the histologic sections. The fact that there is frequently an absence of sufficient gross anatomic evidence to make formation of a diagnosis possible has been pointed out by other workers. Thus, Rothstein and Welt stated that negative gross results at necropsy cannot rule out the possible presence of periarteritis nodosa, for in a significant number of cases the pathologic changes can be demonstrated only after careful microscopic examination of every organ. They stated that the disease may be localized to one organ and that even that organ may reveal only microscopic changes.

We are inclined to agree with those workers who believe that the several diseases which are now classified as "periarteritis nodosa" are only symptom complexes or syndromes and are probably the result of a wide variety of infectious or toxic agents.

It is likewise difficult to determine on the basis of the evidence collected in these two cases which coat of the artery was first involved. It appears likely, however, on the basis of evidence presented by other workers (Mönckeberg, Benda, Ferrari, Walter, and others) that the disease begins in the media.

We have preferred to call this symptom complex "primary arteritis" in the sense used by Karsner to designate inflammation of the arteries in which infective agents are not demonstrable. Most authors agree that the lesions are in the small arteries only and the originally described nodules are very infrequent.

SUMMARY

Instances of periarteritis nodosa in children as reported in the literature are reviewed and reports of two additional cases are added. The clinical aspects of this symptom complex are summarized and discussed. The most common symptoms and signs were found to be: (1) fever, (2) leucocytosis, (3) abdominal and rheumatic pains, and (4) evidence of renal disease. In the two cases reported herein the disease processes present were in wholly different stages. In the first case the arteries were the seats of an acute suppurative process. In the second case definitely regressing lesions with proliferative changes were found. The diseases now classified as "periarteritis nodosa" probably are symptom complexes or syndromes referable to a variety of infectious agents.

We prefer to use the term "primary arteritis" rather than "periarteritis nodosa" to designate the cases we have reported.

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CLINICAL STUDIES WITH VITAMIN K IN NEWBORN INFANTS

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THE relationship of a fat-soluble factor to a hemorrhagic diathesis in newborn infants dates back to the observation of Dam[1] in 1929. In a study of the nutritional requirements of chicks, the hemorrhagic disorder observed was attributed to a lowered blood prothrombin level. The physiologic activity of this accessory factor, called vitamin K, is that of maintaining a normal blood prothrombin level. This vitamin is not a single chemical substance since other closely related compounds also possess antihemorrhagic qualities. Considerable literature has accumulated with respect to the distribution, isolation, and synthesis of vitamin K, and has been adequately reviewed in previous communications by other authors. Clinical studies of Vitamin K in adequately controlling low blood prothrombin levels in the neonatal period are presented in this communication.

During the early part of 1940, studies were undertaken to determine (1) the prothrombin concentration (in terms of prothrombin clotting time) of newborn babies during their first week of life; (2) the prothrombin concentration of the mother at the time of delivery; (3) the relationship of the mother's ante-partum diet to the prothrombin level of her newborn infant; (4) the effect of vitamin K administration in the newborn infant on the concentration of prothrombin during the first week of life; and (5) the effect of the administration of vitamin K to the mother during labor on the prothrombin concentration in the newborn infant.

A total of fifty-four infants and their mothers were the subject of this study. We were led to undertake the study by the death of twins, with massive pulmonary and intracranial hemorrhage which could not be attributed to any factor other than a possible disturbance in blood coagulation. The history of this mother also revealed the death of another infant at the age of 5 days from cyanosis and convulsions. Clinically this was probably a case of intracranial hemorrhage although it could not be confirmed as there had been no postmortem examination. Of the series studied, twenty-eight received no unusual treatment or medication, eighteen received a liquid vitamin K concentrate (klotogen*), and in eight cases, the mothers received vitamin K along with bile salts while in labor. Each cubic centimeter of the vitamin K concentrate contained, 1,250 Almquist units (46,875 Dam

From the Pediatric Division, General Hospital, Kansas City, Mo.
*Abbott Laboratories.

units). The amount administered to the infants was 2 c.c. of the liquid concentrate, while the mothers received 6 c.c. of the concentrate with 6 grains of bile salts.

All infants in this series survived, with the exception of one who died at the age of 28 hours with a severe heart defect. In all but three of the fifty-four cases studied, detailed reports of the maternal dietaries were obtained, in an attempt to show the relationship, if any, between the prothrombin deficiency in the baby and any deficiency in the mother's ante-partum diet.

The method employed for the determination of the prothrombin time was the microprothrombin test of Kato,[2] which is a modification of the original quantitative prothrombin test devised by Quick.[3] This test measures the concentration of prothrombin in terms of its coagulation time. The clotting time is inversely proportional to the concentration of prothrombin.*

TABLE I

AVERAGE PROTHROMBIN CLOTTING TIMES

	MOTHER	INFANT							
		AT BIRTH	1 DAY	2 DAYS	3 DAYS	4 DAYS	5 DAYS	6 DAYS	7 DAYS
Untreated control cases	23.4	38.4	39.9	62.4	51.8	38.6	36.6	29.4	24.8
Infants receiving vitamin K	21.6	46.0	41.1	40.4	34.0	31.2	29.5	28.9	25.7
Mothers receiving vitamin K	24.0	34.2	37.9	36.1	36.6	30.8		22.4	20.6

It will be observed (Table I) that the average prothrombin clotting time of the control infants at birth was 38.4 seconds; those who received vitamin K soon after birth had an initial average prothrombin clotting time of 46 seconds, while the infants born to mothers who received vitamin K during labor had an initial prothrombin clotting time of 34.2 seconds. Following the progress of these infants as represented in Table I, we observe that during the third day the control series had a prothrombin clotting time of 51.8 seconds, those receiving vitamin K had a prothrombin clotting time of 34 seconds, and those infants who received their vitamin K through the placenta had a prothrombin clotting time of 36.6 seconds. It is apparent that the quickest drop in the prothrombin clotting time (indicating an increase of prothrombin concentration) took place in those babies who received vitamin K directly. Even though they started with a higher prothrombin clotting time, they were removed from the zone of potential hemorrhage in a much shorter time. Probably the best course would be to give vitamin K to the mother during labor and to follow it up by administering one or two doses of vitamin K during the first forty-eight hours. The lowest prothrombin level was in that group of babies

*Normal prothrombin clotting time with the method employed ranged between 20 and 25 seconds.

TABLE II

PROTHROMBIN CLOTTING TIME OF MOTHERS AND THEIR NEWBORN INFANTS (CONTROL CASES)

CASE NO.	SEX OF INFANT	AGE OF MOTHER	GRAV. MOTHER	PARA. MOTHER	MOTHER		CORD BLOOD		INFANT													
									NEWBORN		1 DAY		2 DAYS		3 DAYS		4 DAYS		5 DAYS		6 DAYS		7 DAYS	
					PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT
1	M	22	IV	IV	25	2½	40	4	40	1	25	3½			30	3	30	3			25	4		
2	F	18	I	I	20	3	45	3¼	40	1½	30	2	55	3½			40	5			25	3½		
3	F	28	V	V	22	3¾	25	2	SU	2	SU	4	67	4½	50	4½	50	4	30	2¼	35	3		
4	M	37	III	III	17	3	30	2	SU	1	SU	2½												
5	F	21	I	I	20	3	SU	4½	45	4	48	5	150	4	70	3½	45	2	50	2½	60	5	45	2½
6	M	20	II	II	20	3	30	1½	40	3¾	50	4	36	1¾	25	2½	23	3			30	3		
7	F	27	II	II	20	1¼	35	2	SU	1¾	120	5	70	3½	35	1	45	4	40	4½	35	1¾		
9	F	23	III	III	30	4	20	2½	35	¾	35	3	50	1¾	65	2¾	50	5			35	3		
10	M	25	II	II	25	3½	25	2¼	45	1½	40	1	75	2¼	80	4½	32	2¼			20	3		
11	F	25	I	I	25	3½			45	1	65	3	185	3¼	140	6½	35	4			30	4⅓		
13	M	21	IV	III	18	3			45	1¾	45	6	80	4	60	2	45	2½						
14	F	28	I	I	30	3	25	2½	45	3	35	3½	65	4	40	1¾	40	5			38	4		
16	F	25	II	II	20	3½	30	3	40	2½	30	3	35	3½			30	2			25	3¾		
17	M	21	I	I	25	3	30	2½	35	1¾	50	3½	30	4			45	2½			25	2½		
18	F	19	I	I	19	2½			45	2¼	45	4	70	4	40	2	45	2½			30	1½		
19	M	22	II	II	25	1¼	30	1½	33	1½	25	4	35	4	40	1¾	35	3	30	1½	25	2½		
20	F	35	XI	X	28	3	25	2	33	1¼	70	3½	45	3½	50	3½	65	3½	45	3½	40	3½		
21	M	25	II	II	28	4	30	2	35	2¼	50	3½	80	5	50	4½	55	3	45	3½	30	2		
22	F	25	II	II	30	3			35	3½	35	3½	45	4	25	4					25	3		
23	M	22	II	II	30	2½	25	2	45	4	50	4	45	3½	45	3½			25	1¾			15	2
24	M	28	III	III	25	3	23	1¾	40	3½	25	3½	25	3½					25	1½			15	3
25	M	35	I	I	25	2½	25	2	40	3¾	45	4	35	4	25	4					25	3½		
26	M	21	II	II	20	3			35	3	25	3½	30	3½			25	4					25	3½
27	M	24	I	I	23	2½			45	3½	50	4½	75	4	45	3	30	4					19	3½
28	F	37	IX	VI	15	3			35	1	30	3	45	3½			40	3			15	3¾		
30	F	19	I	I	25	3½	30	2¾	35	2	30	3½	70	3½	70	4			40	3½			30	3⅔
32	F	17	II	II	22	3			25	1¾	30	3½					20	3			20	3½		
33	F	21	II	II	25	3			25	2	35	3½					25	3½			25	3		
Average					23.4				38.4		39.9		62.4		51.8		38.6		36.6		29.4		24.8	

PT, Prothrombin time in seconds.
CT, Clotting time in minutes.
SU, Specimen unsatisfactory.

TABLE III

PROTHROMBIN CLOTTING TIME OF INFANTS WHO RECEIVED VITAMIN K

CASE NO.	SEX OF INFANT	AGE OF MOTHER	GRAV. MOTHER	PARA. MOTHER	MOTHER		CORD BLOOD		INFANT													
									NEWBORN		1 DAY		2 DAYS		3 DAYS		4 DAYS		5 DAYS		6 DAYS		7 DAYS	
					PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT
8	M	25	III	III	20	3½	35	4½	35	1¾	40	4½	45	3	35	3½	45	2	40	3½	45	4		
12	M	29	I	I	20	3			30	1	35	1½	40	4			45	4½	35	2½	40	4	30	2
15	F	31	I	I	18	1					45	2½	20	¾										
29	F	17	I	I	30	2½	35	2¼	45	1¾	45	2½	70	3½	40	3½			20	3½			25	3¼
31	M	22	II	II	20	3			180	3	(a) 130	7	35	3½	35	3			27	2½			25	3
											(b) 35	3½												
35	M	24	II	II	25	2			40	2			49	3¼	55	3	32	3			35	3½		
36	F	20	I	I	25	3½			23	3	33	3¾	33	3	30	3	28	2½			22	3		
37	F	18	I	I	20	1¾	20	2½	25	1½	35	3½	35	4	30	3½			20	2½			20	2¾
39	M	22	I	I	20	3½			(a) 70	4⅛	45	3½	30	1	25	3	28	3	22	3¼	23	3¼		
									(b) 125	4														
									(c) 40	2½														
40	M	21	I	I	20	1			30	1½	30	1½	25	2½			25	3					30	3
41	F	21	II	II	25	2½			30	1¾	40	3	35	3½	25	3			30	3¼				
42	F	20	I	I	20	3½			40	2¼	SU	4	SU	3½	SU	3					30	2¼		
43	M	16	I	I	20	3¼			25	3			45	3½	30	3½			37	3½			25	2
44	F	20	I	I	22	3					50	3¾	75	4	35	3½	30	3			22	3		
46	F	23	IV	III	22	2½			32	3½	35	3½	40	4	SU	¾			35	2¾			25	3
47	M	37	IV	III	22	3½			50	3¾	25	3	30	3			33	3			32	3		
48	M	19	I	I	25	3			35	2¼	25	3	35	3			15	3			20	3		
49	F	19	II	II	15	4					45	2	45	1¼	SU	3			SU	3¼	20	1		
Average					21.6				46.0		41.1		40.4		34.0		31.2		29.5		28.9		25.7	

PT, Prothrombin time in seconds.
CT, Clotting time in minutes.
SU, Specimen unsatisfactory.

TABLE IV

PROTHROMBIN CLOTTING TIME OF MOTHERS WHO RECEIVED VITAMIN K AND BILE SALTS IN A SINGLE DOSE

CASE NO.	SEX OF INFANT	AGE OF MOTHER	GRAV. MOTHER	PARA. MOTHER	MOTHER		CORD BLOOD		INFANT															
									NEWBORN		1 DAY		2 DAYS		3 DAYS		4 DAYS		5 DAYS		6 DAYS		7 DAYS	
					PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT	PT	CT
34	F	19	II	I	30	1½			25	1¾	25	3¾	30	3½	35	4	35	2¾					20	2½
38	F	20	I	I	15	3			40	2	43	4½	50	1	35	3½			35	3½			22	3½
45	M	17	I	I	22	3½			24	3½	30	3½	20	3			30	1¾			15	3¾		
50	M	27	I	I	20	2			30	3½	35	4½	32	3			35	3			25	1		
51	M	25	I	I	25	3½			50	1¼	35	3½			35	1	25	3			27	2½		
52	F	17	I	I	25	3			30	¾	30	2½			30	4½					25	3		
53	F	27	I	I	25	3			50	3	70	3	60	3	60	3	40	4	32	3			20	3¼
54	M	23	I	I	30	3¼			25	3¼	35	3½	25	2½	25	2½	20	1½			20	2½		
Average					24.0				34.2		37.9		36.1		36.6		30.8				22.4		20.6	

PT, Prothrombin time in seconds.
CT, Clotting time in minutes.
SU, Specimen unsatisfactory.

whose mothers received vitamin K concentrate during labor. Vitamin K concentrate passes through the placenta and exerts a specific effect on the concentration of prothrombin of the fetus, thus assuring a normal clotting mechanism.

COMMENT AND OBSERVATION ON SPECIFIC CASES

CASE 5.—Female. Pregnancy had been full term, and delivery normal. The mother's diet ante partum was low in milk and fruits. The infant contracted a diarrhea at the age of 5 days, and the prothrombin clotting time rose to 90 seconds, interrupting its downward trend. This may be regarded as an example of increased peristalsis hurrying food through the intestinal tract and retarding the elaboration of vitamin K by bacterial action and interfering with its absorption.

CASE 11.—Female. The birth weight was 4 pounds. At age of 2 days the prothrombin clotting time rose to 180 seconds. Next day it was 140 seconds. The prothrombin clotting time returned to normal quickly, and the infant never showed any signs of hemorrhage. However, the tendency was undoubtedly there, and this may be considered the type of case in which a small ooze incident to delivery might be converted into a massive hemorrhage.

CASE 19.—Male. Delivery was normal. Prothrombin clotting time was not unusually elevated at any time. The first baby of this mother died at the age of 7 days with a cerebral hemorrhage. Close observation of this case was kept. Marked icterus developed, but no tendency to bleed. Because of a normal prothrombin time, vitamin K was not given and no hemorrhage resulted. Without the prothrombin determination and in view of the past history, one would be inclined to give vitamin K immediately after birth. The importance of prothrombin determination in the management of such a case is self-evident.

CASE 31.—Male. Delivery was normal. The infant bled persistently from heel puncture. Prothrombin clotting time at birth was 180 seconds. At the end of twenty-four hours it was 130 seconds. No vitamin K was given up to this time; the infant then received 4 c.c. of vitamin K concentrate, and four hours later the prothrombin clotting time was 35 seconds. Bleeding time became reduced and the bleeding from the heel stopped. No other tendency to bleeding was observed. Along with the drop in prothrombin time, the blood clotting time fell from 7 minutes to 3½ minutes in four hours. At the age of 7 days this baby was circumcised, at which time the prothrombin time was 25 seconds, and the blood clotting time, 3 minutes. No unusual hemorrhage was encountered at circumcision.

CASE 39.—Male. The prothrombin clotting time at birth was 70 seconds; blood clotting time, 4 minutes and 20 seconds. Four hours later the prothrombin time was 125 seconds, and blood clotting time, 4 minutes. The infant received 2 c.c. of vitamin K concentrate, but this was vomited. He was given an additional 2 c.c. of vitamin K concentrate, and four hours later the prothrombin time dropped to 40 seconds, and the blood clotting time to 2½ minutes. There was persistent bleeding from the heel puncture until several hours after vitamin K had been given. No other hemorrhage was noted.

CASE 15.—Female. At the age of 1 day the infant developed profuse melena and vomited bright blood. Before the prothrombin time could be determined, the infant had received 20 c.c. of blood intramuscularly. The prothrombin clotting time when seen by us was 45 seconds, and the blood clotting time, 2½ minutes.

The baby was put on vitamin K concentrate, 10 drops every three hours, and received further blood, intraperitoneally. The prothrombin time at the age of 2 days was 20 seconds, and the blood clotting time, less than 1 minute.

The speed with which the prothrombin level reaches normal can be seen in Cases 31 and 39, the level having reached normal in about four hours.

Maternal dietaries were considered adequate if the mother received an average of three or more glasses of milk daily, cereal daily, meat three or more times a week, and fruit and vegetables daily. It will be observed from Table V that the mother's prothrombin time does not seem to be greatly affected by her own diet, irrespective of its adequacy as judged by the above standard. All patients in this study came from a very low income group. Those whose diets were considered adequate had an average prothrombin clotting time of 24.1 seconds, while those whose diets were not considered adequate had a prothrombin clotting time of 22.4 seconds. The slight difference in the prothrombin level is statistically of no significance. By reference to Table V it can be seen that those mothers with adequate dietaries had infants with low prothrombin levels as often as those with poor diets, and in many cases, a poor ante-partum diet on the part of the mother did not keep the infant from having a low prothrombin clotting time during the first week. Deficiency of the mother's diet apparently had no relationship to the prothrombin level in her newborn infant. Babies of some of the women who had deficient diets ante partum had the most nearly normal prothrombin clotting times at birth. Most of the infants had a higher prothrombin clotting time than normal, but this was unrelated to the adequacy of the mother's diet. No hard and fast lines can be drawn in our present state of knowledge regarding adequacy of diet. Our ideas of minimal dietary requirements are changing continually. Today's adequate diet will certainly be inadequate in the future as the result of a better understanding of those factors which are essential to health, growth, and development. No longer can mere quantity and kind of food be considered the essentials of an adequate diet. What is far more important is the quality of the food considered in terms of vitamins and minerals.

The average prothrombin clotting time of infants whose mothers received a diet considered to be adequate was 36.4 seconds as compared to 37 seconds in those infants whose mothers' diet was judged to be inadequate by the usually accepted standards. In isolated instances (Cases 31 and 39) the prothrombin clotting time of the infant at birth was very much elevated, but in the largest number of cases no difference could be observed. It is probable that if the mother's diet is grossly inadequate she may not have a sufficient amount of vitamin K to transmit through the placenta, but here again other factors must be brought

TABLE V

RELATIONSHIP OF MOTHER'S DIET TO PROTHROMBIN CLOTTING TIME IN NEWBORN INFANT

CASE NO.	ADEQUATE DIET		INADEQUATE DIET	
	MOTHER	CHILD	MOTHER	CHILD
1			25	40
2	20	40		
3			22	SU
4			17	SU
5			20	45
6			20	40
7			20	SU
8			20	35
9			30	35
10			25	45
11	25	45		
12			20	30
13			18	45
14	30	45		
15			18	45
16			20	40
17			25	35
18	19	45		
19	25	33		
20	28	33		
21			28	35
22	30	35		
23			30	45
24			25	40
25	25	40		
26			20	35
27	23	45		
28	15	35		
29			30	45
30	25	35		
31			20	180*
32			22	25
33	25	25		
34	30	25		
35	25	40		
36	25	23		
37			20	25
38	15	40		
39			20	70
40			20	30
41			25	30
42			20	40
43				
44			20	25
45			22	24
46			22	32
47			22	50
48	25	35		
49			15	
50			20	30
51			25	50
52			25	30
53			25	50
54			30	25
Average	24.1	36.4	22.4	37

SU, Sample unsatisfactory.

*This figure omitted from computation.

into consideration. It would appear that, on the whole, the mother's diet is not the deciding factor in determining the prothrombin concentration of her newborn infant.

CONCLUSIONS

An elevated prothrombin clotting time is noted in newborn infants.

An upward swing in the prothrombin clotting time during the first few days of life, with a return to normal by the fourth or fifth day, is substantiated.

A hemorrhagic tendency exists in the newborn infant between the second and fifth days of life, as evidenced by an elevated prothrombin clotting time.

Infants who received vitamin K in the first twenty-four hours do not show an upward swing in the prothrombin clotting time.

As little as 2 c.c. of vitamin K inhibited the upward swing in the prothrombin clotting time.

Mothers receiving vitamin K at least twelve hours before delivery transmit it to their infants, as shown by the inhibition of the upward swing in the prothrombin clotting time.

A normal clotting time on the part of the mother does not preclude a hemorrhagic tendency in her infant.

No relationship could be established between the mother's diet and the prothrombin level of her newborn infant.

The completely adequate diet as we understand it today is not sufficient to protect the child from the danger of potential hemorrhage.

Mothers should be given vitamin K ante partum, and the newborn infant should be given similar medication during the first twenty-four hours.

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ORAL TYPHOID-PARATYPHOID VACCINE

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THE reports of the value of oral typhoid and paratyphoid vaccine are conflicting. Crim and Short[1] found significant agglutination titers in ninety-two of one hundred persons after oral vaccine; however, many of them had had previous subcutaneous typhoid vaccine, and their typhoid agglutination titers were not determined before the ingestion of the vaccine. Lacy and Cohen[2] reported that oral vaccine increased the agglutination titer in only 6.9 per cent of 173 persons who had not previously received subcutaneous typhoid vaccine.

One hundred and nine university students who had not had previous typhoid-paratyphoid vaccine volunteered for our study. Dilutions of their sera 1:10 were set up macroscopically against formolized stock cultures of *Eberthella typhosa, Salmonella paratyphi* and *S. schottmülleri* (typhoid and paratyphoid A and B). Rapid slide agglutinations also were done by the method of Welch and Stuart[3] with typhoid H and O and paratyphoid A and B antigens.* The sera of two persons showed agglutination titers above 1:20 and were not included in this study. The remaining 107 were given one capsule of oral typhoid-paratyphoid vaccine* one hour before breakfast on three successive days. Six weeks after the ingestion of the capsules, the agglutination tests were repeated by the same methods.

Of the 107 sera, only one macroscopically agglutinated the stock *E. typhosa* culture in a 1:10 dilution; two agglutinated *S. paratyphi* (paratyphoid A) in 1:10 and 1:20 dilutions, respectively; and three agglutinated *S. schottmülleri* (paratyphoid B) in a dilution of 1:10. By the slide method, four sera caused agglutination in a 1:20 dilution with typhoid H, two with typhoid O, and none with paratyphoid A or B antigens.

SUMMARY

One hundred and seven university students whose sera did not agglutinate typhoid and paratyphoid A and B antigens and who had not had typhoid-paratyphoid immunization were given oral typhoid-paratyphoid vaccine. Six weeks later, none of them had significant agglutination

From the Department of Pediatrics of Duke University School of Medicine and Duke Hospital, Durham, N. C., with the valuable assistance of Miss Mary A. Poston of the Department of Bacteriology.

*We are indebted to the Lederle Laboratories, Inc., for supplying the antigens, and to Eli Lilly and Co. for furnishing the oral vaccine (Typhoral-Mixed).

titers against typhoid or paratyphoid antigens. Such absence of agglutinins does not prove lack of immunity. However, if oral typhoid-paratyphoid vaccination results in an appreciable immunity, this has not yet been proved satisfactorily, and until proof is established, oral typhoid-paratyphoid vaccination should not be recommended.

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STAPHYLOCOCCAL MENINGITIS TREATED WITH SODIUM SULFATHIAZOLE

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STAPHYLOCOCCAL meningitis is an uncommon form of meningitis in the first year of life, as compared to the pneumococcal, streptococcal, influenzal, and meningococcal types of the disease. Usually it is hematogenous or septic in type and secondary to some focus such as an otitis media. Holt and McIntosh[1] state that it is usually fatal. A moderate number of recovered cases have been reported,[2] with various methods of treatment, such as bacteriophage,[3] gentian violet,[4] and simple drainage.[5] With the introduction of chemotherapy with sulfonamide derivatives, further cases were reported. Michels and Gonne[6] summarized the cases of recovery up to June, 1938, and added one of their own that recovered with sulfanilamide treatment, bringing the reported recovered cases to nine. Since then there have been similar cases[7] in which sulfanilamide and antitoxin were used and one case in which there was recovery with the use of sulfapyridine.[8]

With the advent of sulfathiazole and the discovery of its importance in staphylococcal infections with sepsis,[9] it was hoped that this type of meningitis might be more successfully treated. Dietel and Kaiser[10] were the first to report a recovery from staphylococcus meningitis with the use of sulfathiazole, bringing the total cases reported in the English literature to thirteen.

Since sulfathiazole, however, does not pass readily into the spinal fluid,[11] especially when given by mouth, it has been felt that the drug should not be used in the treatment of any type of meningitis. This is evidently true of the meningeal infections not due to the staphylococcus, especially since the other sulfonamide drugs appear to be more valuable in these other types. Nevertheless, since sulfathiazole appears to be the drug of choice at the present time for staphylococcal infections, if a satisfactory concentration could be obtained in the spinal fluid, it might be expected to be of value in controlling staphylococcus meningeal infections. Spink and Hansen,[11] using sodium sulfathiazole intravenously, succeeded in attaining an appreciable level in the spinal fluid for a short time. Since the drug is rapidly excreted and eliminated almost quantitatively in the urine in twenty-four hours,[12] it is evidently very difficult to maintain by oral administration any level obtained by intravenous injection.

With these thoughts in mind, it was felt that an additional case of apparently uncomplicated recovery from a staphylococcus meningitis

of uncertain source, treated with sulfathiazole intravenously and by mouth, might be of interest. It is hoped that this report may further efforts to obtain therapeutically active concentrations of the drug in the spinal fluid by the use of large doses by routes other than by mouth, so that the treatment of this highly fatal type of meningeal infection might be revaluated in terms of chemotherapy.

R. B., a 7-month-old male infant weighing 22 pounds, was first seen on Sept. 21, 1940, with the complaint of a cold for three days accompanied by fever, which had subsided the preceding day, only to rise to 105° F. The family history was irrelevant and the past history noncontributory, except for a fungus infection of the left ear canal which had been present for some months and which was being treated with gentian violet. This ear infection had not involved the drum but at times had caused a mucoid discharge to appear.

The physical examination revealed an acute nasopharyngitis in addition to the involvement of the left ear canal, the drum appearing thickened but not involved. No neurological symptoms or signs were elicited at this time beyond a slight drowsiness. A blood count revealed red blood count, 4,200,000; hemoglobin, 79 per cent; white blood count, 1,600 with 68 per cent lymphocytes and no abnormal cells. Because of the blood findings and the drowsiness the baby was watched carefully, since it was felt that simple nasopharyngeal infection was not sufficient to explain these findings. That afternoon the temperature rose again, and the baby had a generalized convulsion which immediately prompted hospitalization.

On admission to the hospital with a temperature of 105.6° F., the baby appeared acutely ill and in clonic convulsive spasms, with the body held in slight opisthotonos. A slightly stiff neck was elicited, but no fulness of the fontanel was present. The eyes were directed to the right; the pupils were equal and reacted normally to light; the ears and nasopharynx showed no change. The chest was clear; the heart was normal except for tachycardia; and the liver and spleen were palpable at the costal margins. The extremities were negative; the skin was clear; reflexes were present and equal except for questionable abdominal reflexes. A suggestive Kernig sign was present. The baby was given 3 grains of sodium amytal intramuscularly, and a spinal puncture was done. This revealed a slightly hazy fluid under no increased pressure. The cell count was 214, mostly mononuclears, but the smear showed many staphylococci in clumps. Pandy's test was negative, and a normal (qualitative) sugar test was obtained. The Culture showed *Staphylococcus aureus.*

In view of the fact that no definite focus could be found except the chronic infection in the left ear, a myringotomy was done on this drum with the release of a few drops of serosanguineous fluid, insufficient to culture.

The baby was first placed on sulfapyridine, receiving 3.8 Gm. in the first twenty-four hours; 1.4 Gm. of this was given intravenously as the sodium salt. When it was ascertained that sodium sulfathiazole could be obtained, sulfathiazole was substituted by mouth and supplemented by intravenous sodium sulfathiazole in the dosage as seen in Fig. 1.* A citrated blood transfusion of 200 c.c. was given the second day. Although the temperature dropped during sulfapyridine therapy, it rose again, and the spinal fluid the morning of the second day showed a sulfapyridine level of 3.3 mg. per cent, with a positive smear and culture for staphylococcus, 1800 polymorphonuclear cells, a negative sugar, and a positive globulin test. This suggested that at the time of the first lumbar tap the meningeal infection was

*The sodium sulfathiazole was kindly furnished by Winthrop and Co.

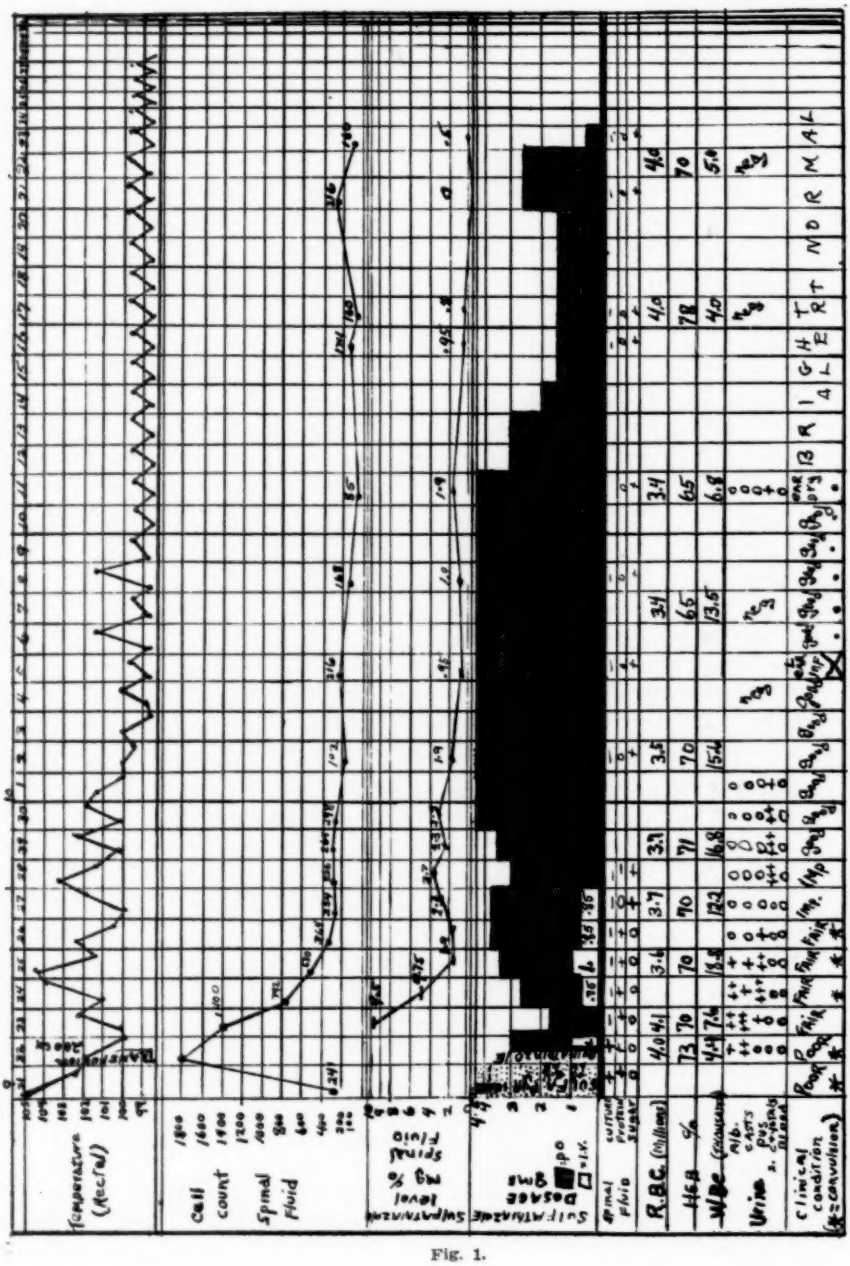
Temperature (Rectal)
Cell count
Spinal Fluid
Sulfamthazine level mg %
Spinal Fluid
Sulfamthazine Dosage gms
Spinal Fluid
R.B.C. (Millions)
Hgb %
W.B.C. (Thousands)
Urine
clinical condition (X=convulsion)

Fig. 1.

just beginning and progressed under sulfapyridine treatment without much hindrance. When sulfathiazole orally and intravenously in large doses was substituted, the child began to improve rapidly.

Fig. 1 shows the details of the dose of the drug and its level in the spinal fluid. Blood culture and blood levels were not taken because of the fact that the meningeal infection was the prominent one which was being treated and a high level was attempted to be reached in the spinal fluid irrespective of the blood concentration.

An ear consultant felt that there was not enough evidence to implicate the left ear as an important focus and believed that no surgical procedure in this region was indicated. The ear dried up quickly but drained glairy mucus again for a few days during the middle of the illness (marked by dots on lowest panel of Fig. 1). This was again interpreted as a flare-up of the fungus infection which subsided with treatment.

The infant's general condition steadily improved after a few generalized spells of twitching occurred during the first few days. His blood count and hemoglobin remained essentially unaffected, although the white cells came up. An erythematous, papular, urticarial-like rash appeared on the twenty-eighth day but faded rapidly when sulfathiazole was discontinued four days later. The culture and smear of the spinal fluid became negative the third day of treatment.

The cells in the spinal fluid did not entirely disappear while under observation, still remaining around 100 mononuclears on discharge, but no other changes were found in the fluid. The infant was sent home apparently entirely cured on the thirty-eighth day, having had a normal temperature for eighteen days while still taking sulfathiazole by mouth and for five days after the drug was stopped. Since returning home, the baby has remained perfectly well.

DISCUSSION

The clinical course is completely presented in Fig. 1. No further comment is necessary except to note that but for the mild, transitory, erythematous rash previously mentioned, a slight bout of diarrhea, and the appearance of sulfathiazole crystals in the urine, there were no toxic reactions such as have been reported due to the continued use of large amounts of the drug.[13] The total amount of sulfathiazole administered over a period of thirty-two days was 101.85 Gm., and at no time was blood seen in the urine. An adequate fluid intake may have aided in this. It is noteworthy that a high total sulfathiazole level of 9.5 per cent was obtained in the spinal fluid on the day following the initial intensive administration and that this level fell while intravenous treatment was continued. However, the level fell much more quickly when the drug was given by mouth alone, in spite of large amounts given by this route. Although it is conceivable that there was still some sulfapyridine in the spinal fluid at the time of the determination of the first sulfathiazole level, the sulfapyridine probably could not account for more than 2 mg. per cent of the total at this time, twenty-four hours after having stopped the sulfapyridine, when a level of 3.3 mg. per cent of this drug was reached.

Subsequent course of events have borne out the clinical impression of complete recovery in spite of the fact that there were still 100 cells in

the spinal fluid on discharge from the hospital. It is still possible, of course, that this child, who is normal mentally and physically at this time, may have a small inactive process walled off at some point in the meninges which might conceivably give trouble later. Nevertheless, the baby is at present perfectly well and happy more than three months after presumable complete recovery.

It is interesting to speculate on the probable cause of infection in this case. Only two possibilities seem to be present, either a hematogenous invasion of the meninges secondary to an acute nasopharyngitis, or an intracranial extension, directly or indirectly, from a low-grade complicating infection of the left ear. The ear appeared so innocuous, however, and healed so readily after myringotomy, that it is doubtful whether the ear infection played any leading role in the development of the meningitis.

The fact that a high level could be attained and maintained for a short time by the intravenous use of the sodium salt of sulfathiazole suggests that these patients should be treated by massive and frequently repeated intravenous injections of the sodium salt rather than by the oral method of administration alone. The intravenous dosage used was recommended by Carey[9] in his review; the dosage per pound of body weight was 1 to 1.25 c.c. of 5 per cent solution of sodium sulfathiazole in distilled water given slowly.

With careful observation for signs of toxicity and renal damage it is possible that much larger doses can be given intravenously every six or eight hours to maintain a therapeutic concentration of the drug in the spinal fluid, since the impression of the relative safety of the drug suggested by other authors,[9-13] especially in children, is borne out by this protocol.

SUMMARY

A case of *Staphylococcus aureus* meningitis in a 7-month-old male infant is reported, with recovery following large oral and intravenous administration of sulfathiazole and its sodium salt.

A high level of sulfathiazole (9.5 mg. per cent) was obtained in the spinal fluid by the use of the sodium salt intravenously. However, this level fell off rapidly, more so when the intravenous root was discontinued.

The relative freedom from toxic reactions, especially on the blood, of 101.85 gm. of the drug given over a period of thirty-two days is noted.

The suggestion is made that repeated intravenous dosages at intervals of six to eight hours should be the best method of obtaining therapeutic concentrations of the drug in the spinal fluid. Oral dosage alone is a poor method for adequate treatment of staphylococcus meningitis with this drug.

Since this report was accepted for publication, a similar report has appeared of recovery in an adult with staphylococcus meningitis treated with sodium sulfathiazole.[14]

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3820 FANNIN

SEVERE INTESTINAL HEMORRHAGE COMPLICATING LOBAR PNEUMONIA

A Case of Dieulafoy's Erosion in a 5-Year-Old Child

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INTESTINAL hemorrhage is rarely considered as a complication in pneumonia, especially in the child. Several reports and discussions of this complication in adults (Dieulafoy, Schneider) and children (Lambrinacos, Aversa) are present in the foreign medical literature. In America only three cases have been described in which gastritis or gastroenteritis with subsequent hemorrhage has complicated pneumonia in the child. It was thought, therefore, of interest to report the following case study, since it describes such an involvement in a 5-year-old child, the youngest yet reported affected by this complication.

B. S. O. (No. A-29841), a 5-year-old white girl, was admitted to the pediatric service of the Grady Hospital on Jan. 23, 1940, with the complaints of fever, cough, and bloody stools.

The father, mother, and six other siblings were in good health. The patient had a normal birth and development. She had had chicken pox at 2 years and measles at 3 years of age. There was no history of blood dyscrasias, dietary indiscretions, or intolerance to any food. Her general health had always been good.

Present Illness.—Five days previous to admission the patient suddenly became feverish, complained of sore throat, and vomited. Following this she became restless and delirious. The next day fresh blood was coughed up, and a slight nosebleed occurred. There was complaint of considerable pain in the left chest on breathing.

On the morning of the day of admission to the hospital, she developed frequent bloody bowel movements. Within one hour the patient had nine stools of what appeared to the mother to be dark blood. Previous to the onset of the diarrhea she had complained of severe pain in the abdomen. The mother estimated the amount of blood lost to be about one pint (500 c.c.).

There was no history of any contact with any communicable disease. There was no history of any foreign bodies having been swallowed by the patient.

Physical Examination.—On admission the temperature was 104.2° F.; pulse, 160; respirations, 40. The patient was a well-developed, acutely ill female child. She was restless and continuously asking for water. The skin was pale, mildly dehydrated, and warm. The lips and conjunctivae were pale. The alae nasae dilated slightly on inspiration. There was limitation of expansion of the left chest, and the patient complained of pain in the lower half of the left chest on inspiration. Dullness to percussion was present in the lower half of the left chest, and in this area bronchial breathing and numerous crepitant râles were heard. The abdomen was distended and tender. On rectal examination tarry feces were seen; there was no rectal tenderness. The pulse was rapid but of fair tone and moderately compressible. The heart tones were soft and slightly distant; no murmurs were present.

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Clinical Data.—The hemoglobin was 32 per cent (5.4 Gm.); red cell count, 1,700,000; white blood count, 13,400, with 64 per cent polymorphonuclear cells, 30 per cent lymphocytes, and 6 per cent monocytes. Examination of the red blood cells showed marked achromia, anisocytosis, poikilocytosis, polychromatophilia, and normoblasts. Microscopic study of a stool on admission revealed numerous red blood cells but no ova or parasites. The benzidine test, done on a portion of the stool, was positive. The urine was negative except for bacteria and a trace of albumen.

A chest roentgenogram showed a partial consolidation of the upper portion of the lower left lobe; the findings were consistent with a partial lobar pneumonia. Examination of the sputum revealed gram positive diplococci resembling pneumococci. On typing, however, no "quelling" occurred with pneumococcus sera I through XXXII.

Course.—On admission the patient was given 500 c.c. of 2.5 per cent glucose in saline subcutaneously. Later a concentrated liquid diet in small amounts was permitted by mouth. Appropriate sedation was administered. The day following admission, with the patient's temperature still elevated, and in spite of the anemia, 0.5 Gm. (7.7 grains) of sulfapyridine was given orally, followed by 0.5 Gm. every six hours. Several blood transfusions were given after donors became available. The fluid intake was maintained by subcutaneous fluids.

The response to sulfapyridine was good, for within twelve hours after starting this medication, her temperature had returned to normal, where it remained for the duration of her hospital stay. A total of 6.5 Gm. (97.5 grains) of sulfapyridine was given over a period of four days. Following the transfusions, the hemoglobin was 60 per cent (10 Gm.); red blood count, 4,950,000; white blood cell count, 7,600, with an essentially normal differential count. The morphology of the red blood cells was normal except for slight central achromia.

Despite the response to sulfapyridine, the patient was in critical condition for the first five hospital days. Her general appearance was poor. The abdomen was distended and tender; and the patient was in a semistuporous state. Following the blood transfusions, her condition improved remarkedly. The melena ceased a few days after admission and did not recur.

After a hospital stay of sixteen days she was discharged in good condition.

A study of the gastrointestinal tract with barium was performed before discharge by Dr. W. Paul Elkin and reported as follows: "A marked pylorospasm persisting over a period of 15 minutes was evident and at the end of 20 minutes only a slight amount of barium was seen in the duodenum. The duodenal cap could not be visualized at the time of fluoroscopy. It was fairly well shown in one of the film studies, however, and showed no evidence of any defect. The small and large intestine showed no evidence of any pathology."

Fluoroscopic and film studies of the lungs and heart at this time showed no evidence of any pathologic change.

During the patient's stay in the hospital the blood culture was sterile. Agglutination tests for typhoid O and H, paratyphoid A and B, *Brucella abortus*, and proteus OX-19 were negative. Cultures of the stools for pathogenic enteric organisms were negative also. The Kahn test for syphilis was negative.

COMMENT

Dieulafoy, Hughes, and Ionescu, independently, in 1899 drew attention to a little described complication of pneumonia, namely intestinal hemorrhage. Dieulafoy listed three cases; all three patients died and were necropsied. One showed acute ulcerations of the stomach; small hemorrhagic foci in the stomach were seen histologically in the other

two. Since he was the first to recognize and describe this complication of pneumonia, the name of Dieulafoy has been attached to it (Dieulafoy's erosion). In 1905 Schneider (cited by Chatard) described ulcerating and other forms of intestinal involvement in a treatise on "The Intestinal Complications in the Course of Pneumonia."

Chatard in 1926, writing in an American journal, reported one case and added eight other cases that he had collected from the literature. His group ranged from the ages of 17 to 51 years. He made the observations that the enterorrhagia occurred, in the majority of the cases, between the fifth and the twelfth day of the pneumonia (oftentimes when the patient was convaleseing) and that the predominating initial symptom was abdominal pain of unusual severity. Chatard believed that the pneumococcus or its toxins was the etiological cause of the ulcerations. He stressed the fact that often the ulcers might be silent and that the intestinal hemorrhage was more likely to occur in the severe cases of pneumonia and in debilitated patients.

In American journals or textbooks little has been written concerning this complication. Rosenblum alludes to statements in Tice and in Osler in which mention is made concerning it, but no cases are described. Osler referred to Dieulafoy's suggestion that the gastroenteritis might give rise to peptic ulcer later in life, providing the patient survived the hemorrhages.

Sanford, Hughes, and Weems (1938) described two cases of lobar pneumonia that were complicated by enterorrhagia, in adults. One of the patients died, and on autopsy a large ulceration (4 cm. in diameter) and six smaller ulcerations were found in the stomach. The other patient survived. The diagnosis in each was pneumonia complicated by acute pneumococcic, hemorrhagic ulcerative gastritis. Pneumococcus typing revealed pneumococcus type four in the sputum of each patient. The lower lobes of the lungs were affected in each case.

Thus far, only three cases have been reported occurring in children in America.

W. Johnson, in 1929, reported the case of a male child, aged 12 years, who had a sudden intestinal hemorrhage of one pint (500 c.c.) during the course of a pneumonia. This patient recovered.

In the same year Rosenblum and Gasul, aware of this complication, reported a case of lobar pneumonia accompanied by melena in an 8-year-old white female child. Their patient had hematemesis and bloody stools five days after the onset of her illness. Physical examination revealed dullness, bronchial breathing, and crepitant râles of the left lower lobe. The red blood count was 1,900,000 per cubic millimeter, and the hemoglobin was 20 per cent (Tallquist). The patient died fifteen hours after admission. On autopsy, lobar pneumonia of the "left pulmonary lobe" and several hemorrhagic gastric erosions were found. The

authors did not mention the fact that theirs was the first proved case in a child. They had reviewed the literature and remarked on the lack of references to this complication.

A more recent case of this complication in a child was reported by Lawrence and Bloxsom in 1939. Their patient, a 12-year-old male, had bloody stools five days after the onset of pneumonia. Physical examination revealed signs of a consolidation in the base of the left lung, and a roentgenogram of the chest showed a central consolidation of the lower lobe of the left lung. The red blood count was 2,000,000 per cubic millimeter, and the hemoglobin was 36 per cent. Bacteria obtained from the sputum and from the stomach contents failed to be agglutinated by pneumococcus sera I to XI. On the ninth day after admission, the temperature dropped by lysis, and on the thirteenth day the patient was discharged. Fluoroscopic and film studies of the gastrointestinal tract, made before the patient left the hospital, showed no pathology.

SUMMARY

Dieulafoy's erosion (gastritis ulcerosa, ulcerative gastritis, hemorrhagic ulcerative gastroenteritis) is a rare and often fatal complication of pneumonia. Five cases of this complication, up to this report, have been described in the American literature, two in adults and three in children; of these, two children have survived. This condition is characterized by the formation of gastric or gastrointestinal ulcers or erosions occurring in the course of pneumonia (usually lobar pneumonia, but may occur in bronchopneumonia, e.g., the second case of Sanford, Hughes, and Weems). No satisfactory reason for the origin of the ulcerations has ever been advanced.

A case of lobar pneumonia accompanied by enterorrhagia (Dieulafoy's erosion) is reported in a 5-year-old female child, who recovered after the use of sulfapyradine and transfusions.

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FOLLOWING THE HYPOCHONDRIACAL CHILD FOR A DECADE

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PROTESTATION of the body in the form of disagreeable sensations is the topic with which the physician spends his life. Pain, dizziness, nausea, fever, insomnia, weakness, etc., are symptomatic protests against trauma, bacterial invasion, the accumulation of toxic products associated with faulty elimination, and the insidious development of degenerative processes in organs and tissues. But, despite the increasing scientific knowledge of lesional pathologic structure, physicians are confronted as they have been from time immemorial with a large group of patients whose body protests are unassociated with any such processes. Internists in diagnostic work estimate the percentage of this group to be as high as 40 to 60 per cent of their regular clientele. They are represented by all ages, and by both sexes in about equal proportions, and are to be found with equal frequency in dispensary as well as private practice. In 1919 the writer[1] attempted to review the literature dealing with medical approaches to this group in connection with a study of sixty patients of the chronic invalid type taken from the wards of the Henry Phipps Psychiatric Clinic of the Johns Hopkins Hospital, from 1913 to 1918. The transition from a neurasthenia-rest cure point of view to a neuroses and psychoneuroses with various modifications of psychotherapy point of view is still in process. In the former we have a traditional medical attitude toward "nerves," which adopts a cut-and-dried mechanical procedure for every case, based upon an outworn pathologic concept that rest, isolation, fattening, and oxygen are needed to build up nerve tissues to withstand strains of life. In the latter we have a medical attitude based upon an attempt to go into the nature of the strain (economic, vocational misfit, marital maladjustment) and the patient's constitutional ability to adapt himself to this strain. For example, a motorman with fifteen years of excellent record as to health and service rendered is transferred to a one-man car, where he has to be conductor and motorman. In the space of two years he averages three months a year of incapacitation for work due to nausea, vomiting, headache, palpitation—symptoms for which repeated and detailed medical examinations can find no cause. Returning this man to his motorman's job results in a complete elimination of his complaints. It would be easy to call him lazy or neurotic. It might be thought that explaining to him the nature of the mechanism of his poor health would be therapeutically effective. But study

From the Henry Phipps Psychiatric Dispensary, Johns Hopkins Hospital.

of the stuff out of which he is made reveals the fact that his particular constitutional endowment could not be expected to behave any differently. His intelligence age is not quite 12 years. He is 45 years old. As a child he was conscientious, serious-minded, very suggestible to environmental influences and stories of illness. A slight cold or stomach upset would keep him in bed longer than the ordinary child would stay there. His mother worried over him, but no more than average mothers do. His wife looks after his health, but no more than the usual wife with no children and only a small home to look after. He had had his present run on our transit system for fifteen years, and had never had an accident or lost more than a day or two at a time from illness until he was transferred from motorman to a two-man job of motorman and conductor. It is not the intellectual equipment alone, or the personality endowment alone, or the chronologic age alone which we can designate as the handicap. But the combination of all three factors in his particular psychobiologic organization makes it impossible for him to acquire the new coordinative habit processes necessary for a two-operation job. Had this man been confronted with this new adjustment earlier in life he might have been able to make it without the development of complaint protests, or he might not have been able to do so. In the sixty cases mentioned, it was interesting to note that our success in removing the chronic invalid pattern of reaction after an average duration of five years from the onset of the present illness was small. Fifteen refused to accept any help that was not in terms of further drug and operative therapy. Of the forty-five who were treated, only sixteen were discharged as "well," and only twelve of these sixteen have never returned to their hypochondriacal habits since leaving the hospital by 1918. In all of the patients in this group, we had good intellectual equipment with which to deal. Practically all of them showed personality traits of hypersensitiveness, timidity, and tendencies toward whining, self-pity, rigid mental attitudes, standoffishness, and tantrums that dated back into childhood. Why is it that re-educational treatment on the wards of a psychiatric clinic "took" on these few patients, and failed to "take" on the majority? Was it the rigorous ward routine or the intellectual understanding of the mechanism, or a combination of both that constituted the active principle of the treatment? It is impossible, of course, to give specific answers to these questions. The trend in psychiatric literature would lead us to believe that helping a patient to something called "insight" into the psychologic mechanisms behind his poor mental health should result in a complete cure of the depression, obsessive fears, anxiety states, and delusional beliefs, as well as hypochondriacal complaining. The longer the physician follows case material over periods of years, the more he comes to realize that insight consists not only of an intellectual understanding of the behavioristic mechanism, but also of an emotional willingness to accept this intellectual concept. The real

question in every case is not only has the patient insight into his difficulties, but is he able to use this insight? Ability to utilize insight is dependent upon the degree of emotional habit training powers of self-discipline which the individual possesses, and also upon his willingness and ability to act upon the intellectual insight acquired. We smile at parents who, without giving their offspring day-by-day training in habit formation, expect them to profit by parental advice born of grown-up experience in the trial-and-error method of life. It is exactly as unreasonable to expect that an adult, even an intellectually precocious one, who has always been emotionally unstable and infantile in his attitudes toward life is going to do a right-about-face in his behavior after the physician has given him an understanding of his psychobiologic mechanisms. The small group of patients who were able to be helped permanently in comparison with the majority whom psychiatry helped only slightly or not at all undoubtedly consisted of persons amenable to re-education of their emotional habit life and mental attitudes relatively late in life, after years of assuming a passive role in the medical and surgical dramas in which they had taken part. This, of course, is the most difficult thing for the chronic invalid.

A qualitative analysis of the psychogenic material to which these grown-ups were exposed and under which they succumbed to hypochondriasis and chronic invalidism represents an average sampling of "the slings and arrows of outrageous fortune" which overtake all human beings. Among these samplings one finds: domestic infelicities of alcoholism, infidelity, in-law frictions, financial strains, worries over increasing family formation, parental domination, sex conflicts, religious conflicts in Protestant-Catholic marriages, thwarted ambitions associated with continuous strivings, failures and odious self-comparisons, sibling jealousies, worries over poor heredity, etc. It is the same etiological material one finds in the background of depressions, manic excitements, schizophrenic reactions, and the psychoneuroses. What determines the type of reaction to which persons succumb? In the constitutional make-up of these sixty chronic invalids, we have an almost equal distribution of ingrowing and outgoing personality traits. But we did find, as I said above, a consistent history of childhood and adolescent evidence of definite reaction to home, school, and social environment registered in a great variety of ways. Again these manifestations vary tremendously and do not seem to bear any consistent relation to the constitutional personality traits. These manifestations comprised temper tantrums, scariness, sullen spells, refusal to go to school, vomiting, fatigue complaints, obsessive worries, fears of dying and fears of family death and other disaster, fear of failure in school, fear of parental disapproval, feelings of insecurity incident to broken homes and other domestic upheavals. These reactions were again not consistent with either an ingrowing or an outgoing personality make-up. Time and again the patient seemed to be the only member of a

group of siblings who reacted to incidents of home, school, or social environment disharmony. In other words, the outstanding fact in reviewing the child and adolescent stories of these sixty adult hypochondriacs seemed to be that they were persons who early showed evidence of extreme sensitiveness to adaptive difficulties of their environment, when other siblings did not do so. One would seem to have to conclude that they were born with a psychobiologic outfit that made them peculiarly susceptible to their environment. The determinants conducive to the hypochondriacal pattern of bending were somewhat easier to allocate. The greatest percentage of these patients grew up in homes with complaining parents, with parents addicted to the doctor habit or the patent medicine dosing habit. The next largest group comprised the medically mismanaged. By this I mean that following an illness or operation, convalescence was delayed by medical uncertainty, "go-slow" advice, and staying out of school for weeks and months, accompanied by increasing environmental solicitude.

It is interesting to compare the results of treatment in these grown-up invalids with the results of early re-educational efforts directed against hypochondriacal tendencies in a group of twenty-two children and adolescents ranging from 3 to 15 years of age. In January, 1923, the writer[2] reported such a study. These children were studied from the standpoint of age, sex, complaint, duration, somatic facts, personality pattern, situational data, and adjustment program. The duration of complaints about them and of their own complaints varied from three weeks to nine years. Their symptom pictures of distress were strangely similar to those of the adult invalid types—palpitation, shaking in the stomach, headaches, pains in the chest, abdomen, and legs, weakness, giddy spells, and fullness in the epigastrium. "I feel all played out." "Sometimes I vomit a lot." "My heart starts beating fast and I can't run." "I get the headache and I have to go in the house and sit down." Behind these cries was comparatively little background of somatic facts as discovered by a pediatrician, laryngologist, ophthalmologist, and laboratory diagnostician. Fifteen patients were physically negative; four showed some eyestrain; two had a tonsil and adenoid condition for which operation was indicated. Needless to say, all these defects were corrected. By far the most significant part of the chart record from an etiological standpoint was found in the columns entitled "Personality Pattern" and "Situational Data." Here again, as in the adult hypochondriac, one found equal distribution of shy, sensitive, whining, easily teased, very suggestible little creatures, and lazy, indifferent, fighting, temperish, sullen children. There were no complaints of mischievousness, sexual delinquency, stealing, or staying out at night. In other words, there was nothing in their behavior that school or home considered annoying or troublesome, or that the layman calls a "problem." In all but one of these twenty-two cases, we found children who expressed complaints that they had absorbed

from an atmosphere charged with hypochondriacal utterance and fear of disease, objectively reinforced by numerous medical contacts and prescriptions, patent medicine dosing, and the medical folklore of neighborhood gossip. With the pattern of these reactions well established through daily contacts of actual behavior, it needed but the catalyzing agent of some circumstance such as a family or neighborhood death or operation, a scary movie, a demotion or failure in school, a fright in the park, a contagious disease, or appendectomy to produce a symptom picture quite baffling to the ordinary approaches of clinical procedure.

The catamnestic data on these twenty-two children and adolescents at the end of eleven years are as follows: Nineteen show absolutely no somatic complaining. Three have turned out very badly; two girls are professional prostitutes, one with gonorrhea and syphilis, and the third is a chronic hypochondriacal invalid resembling her mother. Two of these girls we were wholly unable to help because of maternal attitudes of mental dishonesty expressed in refusal to follow advice or act on suggestions, and persistent traveling to doctors and fortunetellers. Their mothers were promiscuous. The third, the ward of a child-placing agency, was sent back to her mother in Pennsylvania. She was not committed to the agency, which was acting merely in a supervising capacity. All three were mentally retarded, never developing a mental age of over 10½ years. Of the nineteen who have made excellent adjustments, ten were mentally retarded, never going beyond the seventh or eighth grades, and still showing intelligence ages of between 12 and 13 years. Five are single; four are married; one is a widow supporting her three children. Both the married and single are self-supporting and have not been on relief. Nine have graduated from high school; two are attending a university. With the exception of these two still in school, the remaining are self-supporting in business, secretarial work, or industry. When we speak of these nineteen persons as having made an excellent adjustment during the past eleven or twelve years, we base this statement on such matters as whether they have any complaints, whether they are happy and feel a sense of satisfaction in what they have done and are doing, whether they are economically thriving, what their social and recreational activities are. Take F. C., for example, who was referred to us by the pediatrics department in 1921, at 9 years of age, because of weakness, headaches, and palpitation. "All day he hollers, 'Mother, I die,' and keeps his hand over his heart. I cannot get him to school." His condition started six months before we saw him, following a fourth-grade physiology lesson in which he thought the teacher said that a boy who ate an apple, core and all, got its seeds lodged in the "pockets" of his heart and died. His home atmosphere was charged with discord, nervous tension, somatic complaining, and economic stress. His father traveled from physician to

physician for "bladder trouble." One brother had congenital heart disease. (He has since died.) His mother had a fifteen-year record in seven departments of the Johns Hopkins Hospital, with a diagnosis of neurasthenia. Frank had a mental age of 8 years. He was a timid, scary, suggestible boy who hung around the family tailor shop, slept three in a bed, and was teased and knocked about in the schoolyard. The first step was to explain things to his teacher, the school principal, and the school nurse. We took him to school every day for two weeks and saw to it that he stayed there all day. His sleeping arrangements were changed to a bed of his own. We got him sent to camp for two weeks on three successive summers. His father's bladder trouble was found to be a *B. coli* cystitis of which he was cured in our genitourinary department. Frank had a lot of troubles and he liked to run in and out of the dispensary and tell them. We never made any appointments for him to come, but he always knew somebody had a willing ear when he did come back. At the age of 12 he joined the Boy Scouts. At 14 he stopped school in the seventh grade, did fetch-and-carry jobs for four years, and at 18 became apprentice to a printer. At 21 he was a typesetter at $25 a week, and he is still doing it. His Scout work interested him in athletics, and he became active in boys' recreational work. He is a member of the American Boxing Club and has boxed in city and state tournaments. His mental age is 13 years. He weighs 170 pounds. In the meantime, his father has died, and he and another single brother are supporting the mother who is the same complaining, belching woman she has always been.

Or let us take the case of Walter whom we first saw in May, 1922, at 8½ years of age. His parents complained that he was restless, capricious about food, 6 pounds underweight, slept only when given capsules, showed tics of hands and head, would not play with other children, and had been taken out of school for several months by a physician for fear he was on the verge of St. Vitus' dance. His mental age was 9 years. As a young child he was irritable, vomited frequently, and was fussy and jealous of a brother born when Walter was 5 years old. The mother had had St. Vitus' dance as a child, had always been nervous, and had suffered from stomach trouble. She carried this child to kindergarten when he was 4. She took him to numerous physicians. The father stated that during the ten years of their married life he had spent $5,000 on physicians for his wife and Walter. The young brother escaped without complaints or doctoring. But Walter was a child whose habits were so demoralized that we felt it necessary to remove him from his home for six months and board him with a sensible woman in the country. While he was away, we began some parent education on the mother. She was a mentally honest and intelligent woman who really wanted to know how she had got herself and her child into such a situation. By the time Walter returned, she had got herself in hand. She realized that her oversolicitude was

born of traditional ideas of inheritance and a home life practically devoid of any outside interests. She learned to take life easier. Walter has gone on through school, with no further complaints. He is now in a university aiming at journalism as a career, weighs 185 pounds, and takes an active interest in athletics and social activities.

These two boys are examples of what I think we might call excellent adjustment. One is mentally retarded, had only seven grades of formal schooling, came from about as bad a home as one could find, and seemed to show a weak, timid, ineffectual personality. We could not do much to change his home and could make no impression with parent education on his mother's lifelong invalidism. The other boy is of good intelligence, is taking hold of a university education, came from a cultured and comfortable home, and has a mother who has been of great help to him in grasping the principles of parent education involved in their mutual relationships. But he also, during the same number of years prior to his first dispensary contact, seemed to have a weak, whining, unstable personality. These two cases are representative samplings of the child and parent and home material comprising the nineteen boys and girls who, with a little help in early years, have apparently outgrown the hypochondriacal symptoms of their early years. Out of what stuff, environmental and individual, does hypochondriacal material originate? Before attempting to formulate an answer to this question, let us review some of the theoretical concepts advanced by traditional medicine and psychiatrically intelligent medicine concerning this matter. The traditional medical attitude towards hypochondriasis, which was included in the term neurasthenia, has from time immemorial been accepted as nerve exhaustion due to excessive activity of brain function. Flint and Paget and Beard and Weir-Mitchell varied in their hypotheses of pathology from abuse of reflex centers of brain, stomach, and sex organs radiating injury via the nervous system to different parts of the body, to Weir-Mitchell's idea of exhaustion of the lipoids in the central nervous system set forth in his book on fat and blood. They all agreed on the same treatment of rest, sedatives, and building up the nervous system with fattening. The psychiatric approach has varied considerably. Kraepelin regarded hypochondriasis as a symptom of varied mental illness, emphasizing the distorted body complaints in dementia praecox and the nihilistic somatic complaints in depressions. Bleuler had the same emphasis. The psychoanalytic approach has been quite different. Freud classifies hypochondriasis among the actual neuroses, implying an organic basis associated with masturbation. Schilder considers hypochondriasis as a form of narcissism. Adler places it with all the other ills arising from an inferiority complex, with special relation to organic inferiority. Felix Brown,[5] of Maudsley Hospital, London, in a monograph presents the settings of somatic complaints in forty-one patients whom he

studied on the wards and in the dispensary of the Henry Phipps Psychiatric Clinic, from 1934 to 1936. From the psychobiologic standpoint of hypochondriasis as an individual reaction to life difficulties rather than as a disease, he made the following classification:

> "1. Body complaints partly on a physiologic or somatic level, usually associated with anxiety.
>
> "2. Body complaints which have appeared by substitution or conversion of an affect, usually anxiety, with more or less elimination of the affect.
>
> "3. Body complaints with some more or less conscious purpose for the individual—purposive hypochondriasis.
>
> "These three types merge into one another and may be variously mixed in the merergastic reactions.
>
> "4. Body complaints symbolic of something else, some essential conflict of the personality, usually in the parergastic conditions—symbolic hypochondriasis.
>
> "5. Body complaints consistent with a mood disturbance, usually depression."

This study, with its classification, deals with hypochondriasis in adults, as do also the (medical and psychiatric) discussions of this complaint problem outlined above. Now and then there appear facts that give the reader leads back into childhood as the logical spot in which to recognize and treat the beginnings of the body protests pattern of reaction to the strains of life. But comparatively little has been written on the hypochondriacal trends of childhood, so richly deserving of serious consideration by general practitioner and pediatrician and child guidance workers. Kanner[4] gives an excellent general discussion from a psychobiologic standpoint, emphasizing the etiological factors of environmental patterns of grown-up behavior, the suggestibility of individual child anlage, medical mismanagement, and faulty habit training. Fred Allen claims to pay no attention to environmental adjustment and habit training, but focuses therapeutic emphasis on creating opportunities for the hypochondriacally complaining child to find other outlets for his emotional expression, thus learning to right his own small craft as it bounces around upon the troubled waters of a life which he is obliged to meet. Levy,[5] in a paper entitled "Body Interest in Children and Hypochondriasis," recognizes all these factors, but lays great stress upon the relation of hypochondriasis to the development of body narcissism. He says: "Ordinary sensitivities to variations in body form result in certain selection of interests regarding the body, compensatory strivings, and insufficiency feelings, in themselves unimportant in developing hypochondriasis unless utilized by other psychic mechanisms. . . 'Hypochondriacal' symptoms that have their source in castration fears or guilt formation based on sex activity are largely of the anxiety type; sometimes distinctly phobic. . . . All so-called

hypochondriac symptoms appear to be secondary to various neurotic mechanisms except (theoretically) when body pleasure based on the erotogenic zones is unusually reenforced."

In reviewing etiological factors associated with the hypochondriacal reactions in these twenty-two children, no one cause or causes stand out. With the exception of one perhaps, there was no striking affective accompaniment. And even in this case, one hesitates to speak of an anxiety state. It was rather scariness augmented by equal scariness of the father and mother. Like all these boys and girls, he was extremely suggestible, and the trend of the suggestibility seemed clearly determined by somatic worries continually poured out by the grown-up environment. All but one of these twenty-two children came from homes in which one or poth parents were somatic complainers. With parental fear of disease in the child went parental policies of treating the child like an ill person. Medical uncertainty and the failure of medicines, operations, diets, and removal from school and play increased the small patient's whining and weakness and gastric explosions and complete habit disorganization. The situational data starting each particular child on its invalid ways comprised varied facts: desertion of the father, with consequent maternal absorption in the only child; death of a sibling; operation (tonsillectomy and adenoidectomy, appendectomy) and sudden gastrointestinal or respiratory outburst; advent of a second sibling when patient had been the only child; physiology lesson and health talks at school; psychotic outburst in the family; domestic friction between parents over policies of management. In only one child did autoerotism seem to play a causal role. It is hard to consider all these children as showing "neurotic mechanisms." The word neurotic to me implies a fixity of behavior tendencies recurring again and again, indicative of a fundamentally unstable psychobiology. The comparative ease with which these body complaints disappeared and their failure to reappear over a period of more than eleven years, together with the satisfactory adjustment of these boys and girls, would seem to argue in favor of habit lapses on an environmental basis. One hesitates also to speak of their behavior as "purposive hypochondriasis." The escape from school and the monopoly of the limelight in the family circle gave individual satisfaction and pleasure and in that sense were purposive, but one cannot believe that they were deliberate and planned as the term purposive seems to imply. The invalid ways, with their attendant advantages, seem to have developed in every instance from an unwitting drifting with the current of daily complainings and daily parental and medical yielding to the complainings. Therapeutic objectives seemed logically to point toward: (1) the clearing up of medical uncertainties as quickly as possible; (2) the correction of parental attitudes toward the child's behavior as a whole and not merely toward his body protests; (3) the creation of a better understanding between parents and school concerning the child's needs;

(4) an immediate right-about-face in habits of eating, sleeping, going out to play, school attendance; (5) the finding of other satisfactions for energy and emotional expression more attractive to child and adolescent than invalidism. In a few instances it was necessary to take the child out of his home for several weeks, but in the majority of these cases the adjustment occurred with the child in his family setting. Our following of these children has not been what social science and child guidance would call "intensive case work." After the first month or two of re-educational efforts, we let child and family and school alone for several months, making it quite clear that we were at any time attentive to their cries for help, but after all, the job was theirs, not ours. Treatment of children and families of these children, to be sound and lasting, should ever keep in mind the early establishment of child and family independence. The regular traveling of child and family to the clinic doctor and social worker tends to foster a sort of nursing care dependence for guidance and judgment at every step, and embroils schools and teachers in ways that irritate and alienate and give rise to friction between school system and clinic. The mind of childhood expresses itself in imagination, in energy outgo, in joy of action. It is not crushed with grief or torn with introspective complexities. A child senses quickly what a grown-up wants him to say when he is bombarded with questions or trapped into answers, and he says what he thinks his questioner wants to hear, because he desires to please and achieve approval of teacher, parent, physician, or social worker. His words and actions represent largely the amplifications of his imagination and energies upon what he hears people around him say and sees them do. With these natural assets unhampered by inhibitions of "years that bring the philosophic mind," he is ready to start any behavior pattern good or bad with which environment confronts him. In the hands of the pediatrician, the social worker, and the child guidance physician lies the opportunity to interpret his behavior to parents and teachers and community social organizations. Are we seeing the child as the integrated functioning organism that he is, or are we unwittingly playing on his suggestibility to clothe him in complexities of introspective rumination and symbolism that in reality represent adult groping among the shadows of life's insecurities and uncertainties which enshroud our own thinking and living?

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Proceedings

TENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

MEMPHIS, TENN.—NOV. 18-20, 1940

Round Table Discussion on Anemias of Infancy

Chairman: Arthur F. Abt, M.D., Chicago, Ill.
Associates: Robert A. Strong, M.D., New Orleans, La.
William F. Windle, Ph.D., Chicago, Ill.
Secretary: James B. Stone, M.D., Richmond, Va.

Development of the Blood and Changes in the Blood Picture at Birth

William F. Windle, Ph.D.,* Chicago

It is proper to commence a symposium on anemias in infancy with a consideration of the developmental physiology of the blood. It is essential to form as clear a picture as possible of the blood at the end of fetal life and the beginning of postnatal life before discussing anemia in the newborn infant. I should like to define certain normal blood standards for you, but I must warn you at the start that I am unable to do so to my own complete satisfaction. I must plead that investigators have yet to uncover all the necessary facts. You are undoubtedly aware that there is no agreement on what are to be considered the true normal values for red corpuscles and hemoglobin at birth, and that until we have such standards, we will be unable to say with certainty what constitutes anemia in the newborn infant.

The Blood of the Fetus:

Genesis of red blood cells occurs shortly after the formation of the germ layers. It starts in the wall of the embryonic yolk sac and persists there until the second month. Blood formation begins to shift to the body mesenchyme and blood vessels about the fifth week. The liver starts to produce red blood cells in the sixth week, soon becomes the most active erythropoietic organ, and remains so until midfetal life. Erythropoiesis is initiated in the spleen at the end of the second month, and in the bone marrow during the third month. The activities of the various organs overlap and most foci of erythropoiesis are transient. Even in the liver, formation of blood elements stops at birth. Only the bone marrow normally carries it on into postnatal life.

Although some investigators believe that the various blood elements arise from two or three different types of parent stem cells, many now hold that they have one common ancestor, a generalized mother cell, often called a hemocytoblast or hemoblast. This is a large ameboid element resembling a large lymphocyte. Differentiation of red blood corpuscles proceeds through proerythroblasts, erythroblasts, normoblasts, and reticulocytes. Proerythroblasts show the first traces of hemoglobin in

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their cytoplasm, and are the only "red" cells of the blood during the first six weeks of development. After the third month they are confined to the hematopoietic centers. Some authors use the term megaloblast synonymously with proerythroblast. Normoblasts are small cells with pyknotic nuclei and more hemoglobin than erythroblasts; they first develop from erythroblasts in the fetal liver and are the predominant type of red cell in the blood at two months. Erythroplastids, or true red blood corpuscles, arise from normoblasts by fragmentation and extrusion of their nuclei. They make their appearance as spherical forms in the liver at about two months and become the predominant hemoglobin-containing element of the blood during the third month of fetal life.

At three months approximately 90 per cent of the red corpuscles are reticulocytes. The number of reticulocytes diminishes rapidly to 15 to 30 per cent at six months and to only 4 to 6 per cent at birth. About 0.1 per cent normoblasts are found at birth; other types of nucleated cells are not normally present.

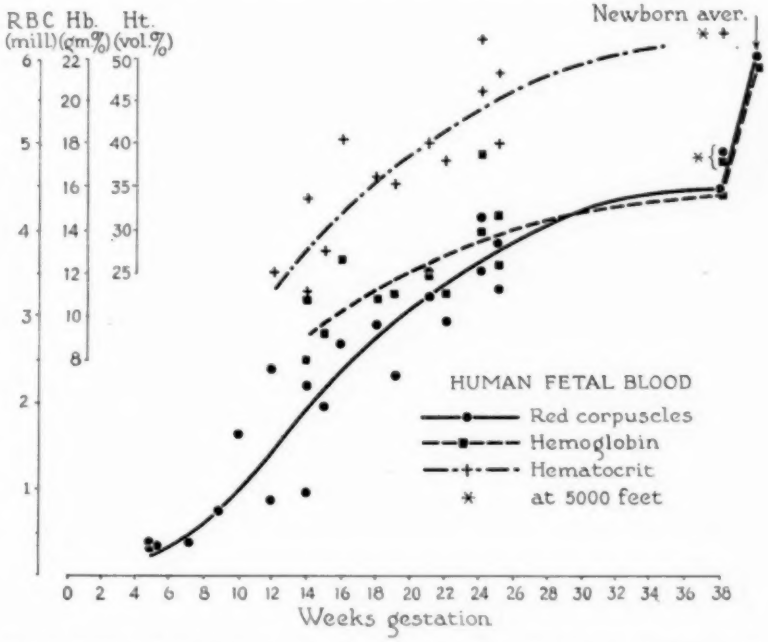

Fig. 1.—The blood picture in the human fetus. (Date from Knoll, 1927; Wintrobe and Shumacker, 1935; Mugrage and Andresen, 1936; DeMarsh, Alt, and Windle, 1940.)

It has been known for many years that the total number of hemoglobin-containing cells, as well as the number per cubic millimeter, increases progressively as the fetus grows; numerical data are limited and no complete systematic study of the blood picture during development has been made in man. All information available for the number of corpuscles and amounts of hemoglobin has been assembled in Fig. 1. The number of red corpuscles in the circulating blood increases from less than 400,000 per cubic millimeter at five weeks to approximately 3.5 million per cubic millimeter at six months. In our laboratory, the average number of red corpuscles in the blood at the end of gestation (from the umbilical cord at the moment of birth) was found to be 4.48 millions per cubic millimeter in thirty-five cases. Mugrage

and Andresen obtained slightly higher values in forty cases, but at an elevation of 5,000 feet. For reasons to be discussed when we speak of changes in the blood picture at birth, the much higher numbers of corpuscles reported in the literature for premature infants as well as for newborn infants cannot be accepted as representative of the true blood picture in the later months of prenatal life.

The amount of hemoglobin in fetal blood is relatively great at a time as early in prenatal life as estimations have been made. In the fourth month it is approximately 10 Gm. per 100 c.c. of blood, increasing gradually to reach 15.7 Gm. at the end of gestation.

Fetal red corpuscles are larger than those of the infant after birth. Great variation among individual corpuscles is encountered. The average diameter of corpuscles at three months' gestation has been reported to be 9.2 μ, and at six months, 8.1 μ in the dry state (smears). At birth the average diameter in dry preparations has been determined to be 7.99 μ by Faxén, although other values have been reported.

The increase in the number of corpuscles during development more than offsets the progressive decrease in corpuscular size. Consequently, hematocrit values rise as gestation proceeds toward term. The mean corpuscular hemoglobin available to transport oxygen is a function of the total number and the volume of red corpuscles, and its concentration within individual corpuscles does not vary. A striking similarity has been described between the normal development of the blood picture and the blood in pernicious anemia patients undergoing continuous and effective treatment with a potent antipernicious-anemia factor.

Establishment of these facts has been made possible by a number of studies on development of the blood picture in the common laboratory and domestic animals. Only enough data are available in human fetuses to indicate that the processes are similar to those in the rat, rabbit, cat, dog, pig, and sheep. The most serious deficiency in our knowledge of the prenatal blood picture is lack of total blood volume determinations. Nothing is known in man. Only in the sheep have accurate estimates been made by an improved colorimetric method.

In viewing the problem of total blood volume in prenatal life, one must not lose sight of the fact that the placental circulation contains a large part of the fetal blood. We cannot consider blood volume in terms of surface area, for the fetus has no surface from a physiologic point of view. We must relate the blood volume to weight of all the tissues through which the blood flows, i.e., the weight of fetal body plus that of the placenta. Blood constitutes about 15 per cent of the weight of the sheep fetus at the end of gestation.

In the sheep, the placenta reaches a maximum size about the middle of gestation, when the fetus, the size of a large rat, has attained only about one-sixteenth of its birth weight. Blood forms a much larger proportion of the fetal weight at this time than it does near term. The absolute amount of blood increases greatly with gestation, but the ratio of blood volume to body weight declines. The amount of blood in the placenta remains nearly constant throughout the last third of fetal life, while that in the body increases several fold. The blood is about equally divided between placenta and fetal body at the beginning of the last third of prenatal life; at term, approximately one-fourth of it is in the placenta.

Data on total blood volume and hemoglobin synthesis in the human fetus are badly needed. The blood mass of the sheep fetus at full term (147 days) was found to have a total hemoglobin content of approximately 80 Gm. At eighty days' gestation the fetus had manufactured only 4 Gm. of hemoglobin, and at 100 days', only about 15 Gm. The last third of gestation therefore, was the period of greatest gain by the fetus. The pregnant sheep showed a slight loss of hemoglobin at the end of the first third of pregnancy. This was gradually regained and there was no reduction of the mother's hemoglobin during the time the fetus was synthesizing it so rapidly.

In the human fetus at birth we know that the placenta contains a large portion of the total blood mass. From 50 to more than 200 c.c. of blood have been recovered from placentas for "blood banks." It is natural for the newborn infant to retrieve most of this from its placental circulation if severing of the cord is delayed for a sufficiently long time. It was found that the average amount of blood in the placental vessels in one series of 120 cases was 105 c.c. Fifty-one per cent of this flowed into the infant from the placenta in the first minute after delivery; 79 per cent reached the child in the first five minutes, and 91 per cent in the first ten minutes.

Total blood volume has been estimated in the human newborn infant by the vital dye technique. An average of 531 c.c. of blood was found in twelve infants three to twenty-four hours after birth. This was 15.5 per cent of body weight. However, we do not know that this accurately represents the true total blood volume at the end of gestation, because the investigators failed to say whether or not placental blood had been allowed to return to the child before the umbilical cord was clamped. If 531 c.c. is the total blood volume at the end of gestation, it is evident that the placental circulation in man contains, on the average, approximately one-fifth, and in some individual cases more than one-fourth, of all the fetal blood.

The physiology of circulation and respiration in fetal life has been but poorly understood until recently. Most of us have held that the fetus gets along quite well with little oxygen and that the blood reaching it from the placenta has a high degree of unsaturation. Apparently this is far from the true condition.

Perfection of experimental methods has made it possible for Barcroft and his colleagues to withdraw blood samples from umbilical vessels of sheep fetuses without delivering them. The blood of the umbilical vein (going to the fetus) was found to be more than 90 per cent saturated with oxygen in half of the experiments. Saturation was greatest during the middle third of gestation. Upper limits of 90 per cent in the ox and approximately 84 per cent in man have been reported. At the time of parturition the values are somewhat less. What are the mechanisms that account for such a high degree of oxygenation? Gas tensions in the placenta are certainly not so high as in the lungs.

In the first place, it has been demonstrated that certain anatomic arrangements of the blood streams of the placenta favor an efficient transfer of the blood gases. One can picture the placental circulation rather simply: A well-oxygenated stream of the mother's blood enters the placenta and comes into intimate contact with the fetal blood stream, poor in oxygen. The two do not mix, but the degrees of contact differ in various species of mammals. One might think that the two streams should come into equilibrium in respect to the tensions of their blood gases, the umbilical vein blood becoming as saturated or as unsaturated as the uterine vein blood of the mother, and that the umbilical vein blood of the fetus should become progressively darker as gestation proceeds toward its termination. Actually this does not happen. It has been found that the maternal and fetal capillary streams, instead of flowing parallel to one another, flow in opposite directions in the rabbit placenta. A similar arrangement has been found in some other mammals. Thus the fetal blood is able to come into equilibrium, not with the maternal venous blood, but with that at the arterial end of the maternal capillary bed. The mechanism is illustrated in Fig. 2. That a similar mechanism operates in man is unproved.

The placenta reaches its maximum size while the fetus is still growing and building hemoglobin at a rapid rate. The cessation of gain in placental size is compensated by an increase in efficiency of the fetal circulation. In the sheep, the volume of fetal blood traversing the placenta increases in proportion to fetal weight. An increase in fetal blood pressure throughout pregnancy helps regulate the amount of blood passing through the placenta per minute. Near the end of gestation, 284 to 568 c.c. per minute flowed through these vessels. On the maternal side of the placenta, there appeared to be a somewhat less marked increase in volume of blood

flow, except near term, when it was reduced. Oxygen consumption by the fetal tissues is constant throughout the last third of gestation in the sheep. It is estimated to be 0.0043 c.c./g/mm.

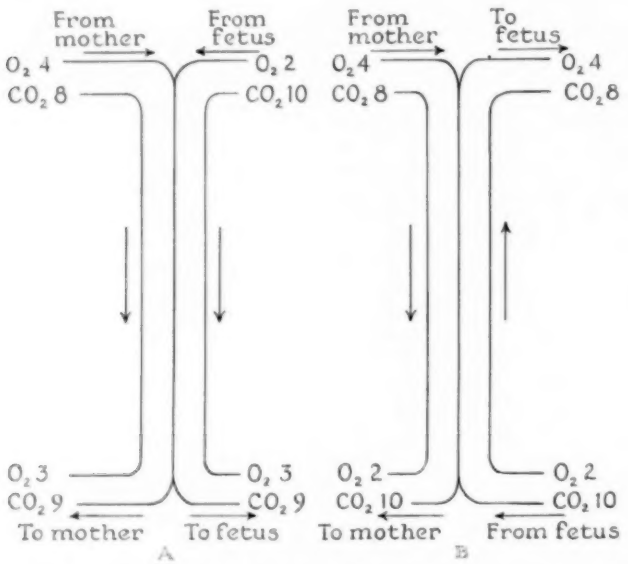

Fig. 2.—The exchange of oxygen and carbon dioxide in the placenta. If the maternal and fetal capillary streams course in the same direction (*A*), blood returning to the fetus will be as venous as that returning to the mother. But if the streams course in opposite directions (*B*), it will come into equilibrium with that of the mother's arterial blood. (From Windle, 1940; redrawn from Mossman, 1926.)

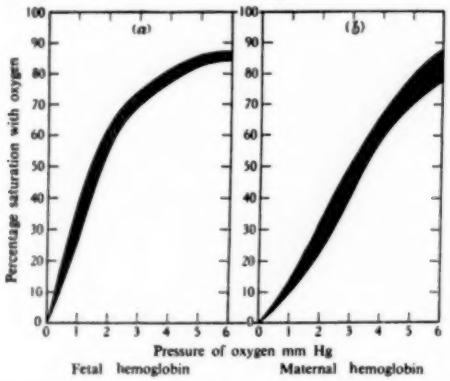

Fig. 3.—Oxygen dissociation curves for fetal (*a*) and maternal (*b*) hemoglobin in the sheep. Limits fall within the dark areas. Approximate temperature was 19° C.; pH, 9.3. (From Windle, 1940; after Hill.)

Another mechanism enables the fetus to obtain oxygen readily in the placenta under the pressure conditions prevailing there. The hemoglobin of the fetal blood differs chemically from that of the adult. The difference is such in the species which

have been studied that oxygen is taken up with greater avidity at low partial pressures by the fetal than by the maternal hemoglobin. The differences can be seen by comparing oxygen dissociation curves for solutions of fetal and maternal hemoglobin, such as those shown in Fig. 3.

In the goat during the last half of gestation fetal hemoglobin becomes 60 per cent saturated with oxygen at a pressure only one-half of that required for the same degree of saturation in the mother, the hydrogen ion concentration of the solutions being the same. Differences become less noticeable as parturition is approached, and by five weeks after birth the kid's hemoglobin attains adult characteristics. Similar differences between fetal and maternal hemoglobin solutions have been reported in rabbits and even in chicks of the domestic fowl. A very pronounced avidity for oxygen at low gas tensions has been demonstrated in whole blood of calves near term. It was shown that dissociation curves of whole blood in relation to those of the mother are inexplainable solely on the basis of greater alkalinity of the mother's blood. They are governed by true chemical differences in the hemoglobins.

The human fetus at full term may differ from others, for it has been reported that its hemoglobin in dilute solutions takes up oxygen less than does that of its mother. Nevertheless, buffered (pH 7.4) suspensions of fetal corpuscles, like whole fetal blood, become more highly saturated with oxygen at low partial pressures than similar suspensions of the mother's corpuscles. No data are available for the human fetus prior to full term. Species differences in avidity of the hemoglobin for oxygen may be related to the degree of maturity reached at birth. Other evidence points to a true difference between fetal and maternal hemoglobin.

The significance of the blood picture at the end of fetal life is becoming clear. The full-term fetus does not possess a polycythemia ascribable to a high degree of venocity of its circulating blood. These concepts are wrong. At the end of prenatal life there are actually fewer corpuscles per unit volume of blood than in the adult. The blood received by the fetus from its placenta is essentially arterial blood. It is true that fetal hemoglobin values at term are in excess of those encountered in the normal adult. This is due to the fact that the corpuscles, although decreasing in size progressively throughout gestation, are still larger than adult corpuscles. Special anatomic and chemical mechanisms, already described, enable the fetus to obtain oxygen with great avidity in a placental environment of relatively low oxygen tension and without the necessity for developing an excessive number of red corpuscles. It seems more probable that blood development occurs as it does because hematopoietic centers respond to some intrinsic, perhaps hormonal, growth factors, than that it develops in response to a threat of asphyxiation.

The Blood Picture in Early Infancy:

Much has been written concerning the blood in infancy. Nevertheless, our knowledge today is incomplete, and many controversial points remain to be clarified. In reviewing the voluminous literature on the blood picture in the newborn infant, one is impressed by the lack of agreement as to what values for the number of red corpuscles and amount of hemoglobin constitute normal standards. Differences are often too great to be accounted for on the basis of normal race or individual variations. One suspects some other factors. The exact source of blood and the methods of taking samples are often omitted in reports. The methods of estimating hemoglobin vary widely; hemoglobin, frequently reported in per cent, cannot always be transferred into grams per 100 c.c., and what may be even more significant, authors seldom state whether the blood was drawn from infants allowed to retrieve their placental blood or from those deprived of it by immediate clamping of the umbilical cord at birth.

Some investigators have held that a true polycythemia exists at birth, but others have failed to substantiate this. The average figures reported for the number of

red corpuscles and the amount of hemoglobin vary all the way from those encountered in normal adults to average values as high as 6.5 million red corpuscles per cubic millimeter and 23 Gm. of hemoglobin per 100 c.c. Individual counts greater than 7 million red corpuscles per cubic millimeter are not uncommon.

Before we can arrive at a standard, it must be realized that the number of corpuscles in a cubic millimeter of umbilical blood at the end of gestation differs from that in the same quantity of blood drawn from the infant less than an hour after birth. Dr. DeMarsh, Dr. Alt, and I have investigated this subject recently. The average difference amounted to 1 million corpuscles in one group of twenty-five infants whose cords were clamped immediately at birth, and to more than 1.5 million in twenty-five whose cords were not clamped until placental blood had passed into the infants at birth. Corresponding hemoglobin differences were encountered (3 Gm. in immediate clamping and 6 Gm. in the delay group).

The explanation of these surprising differences is difficult. We thought at first that there might be a discrepancy between capillary (infant's heel) and venous (umbilical vein) blood. This was suggested by several observations in the literature. Waugh and his colleagues reported from 15 to 15.5 Gm. of hemoglobin in blood from umbilical cords as well as from venous sinuses during the first week of life. Osgood found, on the average, 17.2 Gm. of hemoglobin per 100 c.c. of venous sinus blood during the first four days of life. This declined to 16 Gm. by the tenth day. Red corpuscles averaged 4.6 million per cubic millimeter. These values do not differ greatly from our own and others' results on umbilical cord (venous) blood, but they are considerably lower than those we obtained from the heel capillary blood after birth.

Haden and Neff compared capillary and venous sinus blood in newborn infants and found red corpuscles more numerous in capillary blood. Duke and Stoffer discovered a similar discrepancy between capillary and venous blood of adult patients with pernicious anemia. This blood, like that of the newborn infant, contains many large corpuscles. They suggested that these large corpuscles occluded capillaries and led to concentration of corpuscles there. Other investigators have failed to confirm the difference between capillary and venous blood in the newborn infant. Mugrage and Andresen reported that lower values were obtained on cord blood than on venous blood at birth.

We have made comparisons between samples obtained from the superior sagittal sinus (or jugular vein) and form the heel capillaries in six normal infants, as well as from the cubital vein and finger blood of one adult with pernicious anemia. Our results show no significant difference between capillary and venous blood in respect to the number of red corpuscles. Furthermore, the hemoglobin values obtained in venous blood of infants are comparable with the average of those obtained from heel blood.

It is doubtful that the sudden increase in the number of corpuscles in the infant's circulating blood at the time of birth is due to a difference between capillary and venous blood. Postnatal dehydration is an unlikely explanation because the change often takes place in less than half an hour. A possible explanation may be found in the relationship of the spleen to this phenomenon. Polycythemia due to splenic contractions during emotional excitement has been observed in the cat. In prenatal life the smooth musculature of the fetal body is less active than that of the individual after birth. Perhaps initiation of splenic contraction throws a significant reserve of concentrated corpuscles into circulation. This would cause the difference between umbilical cord and heel blood that we have observed. It is interesting to note that Horváth and Hollosi found more red corpuscles and hemoglobin in the infant's umbilical artery blood than in that from the umbilical vein; heel blood drawn at birth showed even higher values.

Granting that the number of corpuscles and amount of hemoglobin per unit volume of blood increase sharply at birth, we are still unable to determine standard

values without accurate knowledge of total blood volume. The height of the rise at birth appears to be related to the amount of blood the infant recovers from its placental circulation. The results of several investigators suggest this, and recent study by DeMarsh, Alt, and myself shows it even more clearly.

The umbilical cords were clamped as soon as possible after normal delivery without anesthesia in one series of twenty-five healthy newborn infants; the time elapsing was thirty seconds or less. In another twenty-five infants the cords were not clamped until the placentas had separated from the uteri. This usually occurred within ten minutes after delivery. It was found that the baby received an additional amount of blood between the time the cord stopped pulsating and the time the uterus contracted firmly, with separation of the placenta. This was measured in ten instances and was found to average 62 c.c. Only a few cubic centimeters of blood at best can be obtained from the umbilical cord after separation of the placenta. In fact, we were unable to draw enough blood from a number of the cords to give adequate determination of hemoglobin and corpuscles.

Red corpuscle counts and hemoglobin determinations were made on cord blood and on blood from the heel of the infant twenty to seventy-five minutes, one day, three to four days, and six to seven days after birth.

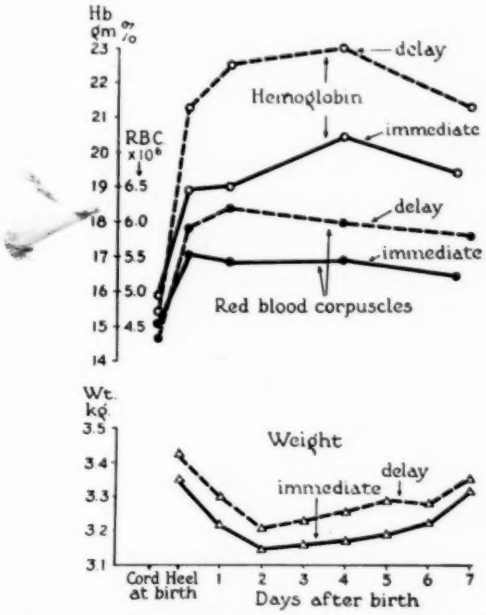

Fig. 4.—Average number of red corpuscles, amount of hemoglobin, and body weights of infants from birth to the seventh day. Solid lines, infants whose cords were clamped immediately; broken lines, infants on whom clamping was delayed. (From DeMarsh, Alt, and Windle.)

Averages of our results are shown graphically in Fig. 4. The average values for cord blood were 4.5 million red corpuscles per cubic millimeter and 15.7 Gm. of hemoglobin per 100 c.c. They were approximately the same whether the cord was clamped early or late. Within twenty to seventy-five minutes after birth, the values in blood from the heel were much higher. Henceforth throughout the week the infants whose cords were clamped immediately had significantly lower corpuscle and

hemoglobin values than those whose cords were clamped late. During the first week the former group averaged 5.45 million red corpuscles per cubic millimeter and 19.5 Gm. of hemoglobin per 100 c.c., whereas the latter group averaged 6.01 million red corpuscles and 22.1 Gm. of hemoglobin. The difference between the two groups at each age period was statistically significant, especially at one, three to four, and six to seven days after birth.

In view of the facts that the placenta contains one-fifth to one-fourth of the total fetal blood at birth and that all this blood does not pass into the infant at birth until after uterine contractions have had a chance to compress the placenta, we believe that the rather common practice of promptly clamping the cord at birth should be condemned. Of course, this will make it impossible to salvage placental blood for "blood banks." However, the collection of usable quantities of placental blood robs the newborn infant of blood which belongs to him and which he retrieves under natural conditions.

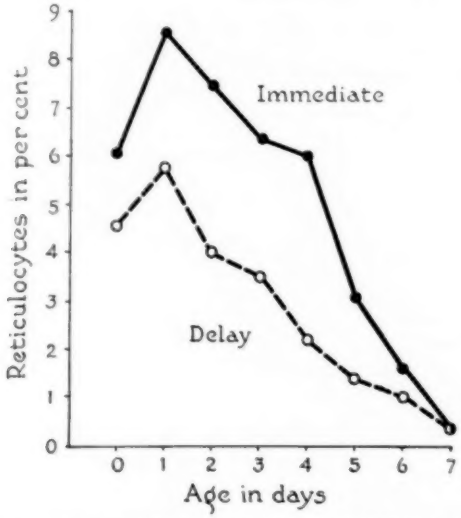

Fig. 5.—Average percentage of reticulocytes in the blood of infants from birth to the seventh day. (From DeMarsh, Alt, and Windle.)

Immediate clamping of the cord is comparable to submitting the infant to a rather severe hemorrhage. It appears to result in increased erythropoiesis which is reflected in an increase in circulating reticulocytes. Most observers have reported the reticulocyte count at birth to average about 4 to 6 per cent, decreasing rapidly to less than 1 per cent at the end of the first week. Some have reported a slight rise on the second day. But no one previously has made comparative studies of the reticulocyte count in the newborn infant after early and late tying of the cord. Our own results in such a study are recorded in Fig. 5. This illustrates average values in six infants whose cords were clamped immediately and in six whose cords were clamped after delay. When the cord was tied immediately, reticulocytes reached an average peak of 8.6 per cent at twenty-four hours and did not fall below 6 per cent until the fifth day. When tying of the cord was delayed, reticulocytes averaged only 5.8 per cent at their peak in twenty-four hours and then fell to 4 per cent in forty-eight hours. A more active blood formation when the cord is clamped early than when it is clamped late is suggested by the higher and more sustained rise in reticulocytes in the former group.

I believe I have reviewed enough data on the blood picture during prenatal and early postnatal life to indicate to you possible relationships between developmental conditions and anemias in infancy. A great need for more accurate standards is evident. When we know something about total red corpuscle and hemoglobin mass at birth and more about the blood picture throughout early life, we will be better able to determine what are departures from normal.

One can easily imagine that loss of nearly one-fourth of the total blood volume in the newborn infant may sometimes be critical. In the latter part of the nineteenth century Engel reported twice as great a mortality in premature infants whose cords were tied early as in those whose cords were tied late. The proportion of fetal blood in the placental circuit is higher in the premature infant than it is at full term.

It is evident from our recent studies that deprivation of the newborn infant of its placental blood may lead to iron deficiency in infancy. Fullerton and Stearns and McKinley have recently called attention to the fact that the principal iron reserve of the newborn infant is in the circulating hemoglobin rather than in the tissues. Iron liberated during blood destruction is stored in the tissues and utilized as needed for hemoglobin formation. The amount of iron lost to the newborn infant in 100 c.c. of placental blood prevented from reaching the child from its placenta is 54 mg. This is enough iron to lower the hemoglobin in a 4-month-old infant from 12 to 9.3 Gm. per 100 c.c. of blood. Therefore, it seems possible that loss of placental blood may be an important factor predisposing infants to anemia during the nursing period.

Another question to which considerable discussion has been given in the literature is the possible relationship between maternal iron deficiency and anemia in the newborn infant. It has been proved that the brief period of rapid hemoglobin synthesis in the sheep fetus has no appreciable effect upon the total hemoglobin of the mother. In fact, the mother's total hemoglobin mass increased slightly during this period. This does not prove that a similar condition prevails in man because placental transmission is different in the two species.

The effect on fetal rats of iron-deficient diets fed to the mother has been reported. The first pregnancy brought on marked depletion of maternal liver iron, but there was no anemia. With the advent of a second pregnancy, an anemia did appear. The first litter of rat pups had normal hemoglobin values, but a reduction in total iron of the entire body by about one-half the normal was evident. The second litter exhibited a reduction of the hemoglobin of the blood, and the total iron content was only one-fourth normal. This work seems highly significant.

Some investigators have reported that anemia in pregnant women is associated with iron deficiency in the human fetus. Infants born of anemic mothers may exhibit hypochromic anemia in the first year of life. However, one suspects that this may have been related to deprivation of the placental blood at birth, a factor which was not controlled in the studies. We will have to obtain more information concerning the normal blood picture, and be certain that the infant starts life with all his available blood, before we can prove that anemia in the mother is related to iron deficiency in the child. Furthermore, it will be necessary to have adequate clinical histories of all infants used in studies of this kind, because between birth and the time an anemia manifests itself there are many factors which can influence the infant's iron and copper metabolism.

DISCUSSION

The average values for red corpuscles and hemoglobin from cord blood were approximately the same whether the cord was clamped early or late. Within twenty to seventy-five minutes after birth, the values in blood from the heel were much

higher. Subsequently throughout the first week the infants whose cords were clamped immediately had significantly lower corpuscle and hemoglobin values than those whose cords were clamped late.

QUESTION.—How long should clamping of the cord be delayed?

DR. WINDLE.—Until the pulsation has ceased, and until the placenta has separated from the uterus. It is not sufficient to wait only until pulsations have ceased, for then there is still more than half of the placental blood in the placental circulation. Milking of the cord is, in most cases, probably unnecessary; we delayed oftentimes five, six, or ten minutes, rarely more than ten minutes. That seems to be sufficient time for all, or the greater part, of the blood to flow naturally back to the child.

DR. R. N. ANDREWS, MANKATO, MINN.—How do you account for blood's being transferred to the fetus after the cord has stopped pulsating?

DR. WINDLE.—Pressure by the contracting uterus forces the blood out of the placenta.

DR. L. W. DIGGS, MEMPHIS.—What is the effect on the prothrombin time?

DR. WINDLE.—We did no prothrombin time and no bleeding time on these infants.

QUESTION.—Is there any objection by the obstetrician to delay in clamping of the cord?

DR. WINDLE.—I have not heard any objection directly from obstetricians. It is not too much to expect them to wait a short period of time, ten or fifteen minutes under ordinary conditions, and especially when they have adequate help in the operating room.

The matter of early and late tying of the cord has been a forgotten question. In the latter part of the last century it provoked a great deal of discussion in continental Europe, especially in Germany and Austria. In turning back to the old literature, we find many reports on the question of the benefit of early and late tying, although there was nothing in those reports that gave us any great help on this immediate question of comparison of hemoglobin and red blood cell groups.

QUESTION.—What difference is there in the blood picture in the premature and the full-term infant?

DR. WINDLE.—We haven't been able to compare the blood pictures in viable premature infants with those in the full-term infants. The reason is that we have no values taken from the umbilical circuit in the premature infant. All the values have been taken from the infants in the first, second, and third days of life. The same factor operates in viable premature infants to raise the hemoglobin and red blood cell level that operates in the full-term infant.

Splenic contraction, and perhaps the pouring out of concentrated corpuscles from other organs, must take place in the viable premature infant as well as in the full-term infant. It is important to emphasize again that the premature infant has more of its total blood in the placenta, that is, a larger proportion of it in the placental circuit, than does the infant at full term. Perhaps that was the reason that Engel, ten years ago, found that the premature infants whose cords were tied promptly at birth had a 50 per cent greater mortality than the premature infants whose cords were tied late.

DR. H. J. MORRISON, SAVANNAH, GA.—What is the comparative degree of jaundice in infants with cords tied early and those with cords tied late?

DR. WINDLE.—We anticipated that we would see a difference in the degree of jaundice in the two series of infants. We did not do chemical determinations, but we did observe all the infants carefully, looking at the sclera and general skin color. We were surprised to see no significant difference in the two groups, although we did observe jaundice in a number of individuals. In the ones whose cords were tied late, we found three with rather marked jaundice. If I remember correctly, in the ones whose cords were tied immediately, we found five with jaundice. In the series of fifty-three cases which we had, this is not a significant difference.

QUESTION.—Is this directly opposite from that which you expected?

DR. WINDLE.—We would have expected to find more of the infants who got all of their placental blood showing jaundice, but we did not find a significant difference. The jaundice we did see was probably a physiologic jaundice.

DR. M. I. PIERCE, EVANSTON, ILL.—Was a physiologic anemia noted when there had been delayed clamping of the cord?

DR. WINDLE.—The cases were not under observation long enough for this to be determined.

DR. H. G. PONCHER, EVANSTON, ILL.—Do you feel that the analgesic given to the mother has any relationship to the arterial dissociation in the newborn infant?

DR. WINDLE.—Only two of our patients received any analgesic, and each of these received only 2 grains of nembutal.

DR. C. A. SMITH, BOSTON.—What is the relation of the infant's hemoglobin to that of the mother?

DR. WINDLE.—There is no definite relation between the hemoglobin value in the mother and her newborn infant except that the infant's hemoglobin is more often higher than the mother's. Infants born of anemic mothers and exhibiting hypochromic anemia later in the nursing period may be suffering from iron deficiency due to deprivation of placental blood at the time of birth, caused by too early clamping of the cord. Anemia of the mother does not necessarily mean that the infant will be anemic.

DR. H. F. GARRISON, JACKSON, MISS.—If there is very little relationship between the diet and care of the mother and the red blood cell count and hemoglobin of the infant, what is the relation of the blood picture of the infant to that of the mother?

DR. WINDLE.—The evidence does not indicate that anemia of the mother determines the red cell and hemoglobin values in the infant. The loss of placental blood would seem a more important factor relative to anemia in the infant.

CHAIRMAN ABT.—What is the difference in the chemical nature of the hemoglobin of the mother and the infant at birth?

DR. WINDLE.—The hemoglobin of the fetus has a greater avidity for oxygen and reaches a higher degree of saturation under the same oxygen tension than does that of the mother or of the infant after birth. This is also true of fetal corpuscles. The evidence points to a true chemical difference between the fetal and maternal hemoglobin.

QUESTION.—What is the explanation of the greater avidity for oxygen shown by the fetal hemoglobin?

DR. WINDLE.—The further the fetus is from term, the greater is the avidity of its hemoglobin for oxygen and the less readily does it give up its oxygen to the

tissues. There is a spectroscopic as well as chemical difference in the hemoglobin of the fetus, although it is not known exactly what this difference is.

DR. W. R. PHILLIPS, ELMIRA, N. Y.—Why worry about placental blood if it is destroyed early in the neonatal period?

CHAIRMAN ABT.—Iron content of the cell is not lost to the extent that pigment is, so that there is a reserve storage of this material in the body.

DR. PHILLIPS.—Is iron all that is lacking in infants who develop anemia?

CHAIRMAN ABT.—Iron is stored, and possibly other products of cell hemolysis. Needed material other than iron is fairly well supplied in the milk.

DR. PHILLIPS.—Some don't respond to iron.

DR. WINDLE.—If the anemia were due solely to an iron deficiency, it would probably respond to iron therapy.

CHAIRMAN ABT.—There might be an interference with the function of the blood-forming organs.

DR. WINDLE.—If the baby does have difficulty in utilizing iron given in its diet in the early period in postnatal life, then that is all the more reason that the obstetrician should see that it goes into this period with all the iron possible available. The baby, in extreme cases, may lose as much as 200 or more cubic centimeters of blood if the cord is clamped immediately at birth. That would be over 100 mg. of iron. We must think of that iron as retained in the baby's body, as suggested, because it does not excrete it. I think everybody will admit that it would be very difficult to replace that iron in the baby by feeding it during the nursing period. There's a moral there, to see that the child doesn't lose the iron.

DR. M. C. PEASE, NEW YORK CITY.—Does he really throw away his plasma too?

DR. WINDLE.—I wonder how much he really throws away—whether he really throws away anything. I have a feeling that he utilizes a good deal of this hemolyzed blood, not only the iron, but perhaps some other things, copper and other factors in the blood that he hemolyzes. I don't think of that as waste material at all. I think that it enters definitely into the economy of the individual in the weeks that follow. In regard to the comment, there is a certain amount he does lose because of bile pigments in the urine.

DR. STRONG.—Anemia means a deficiency in red blood cells as well as hemoglobin, and may result from various factors. Blood destruction is going on all the time, and if there is not adequate replacement, anemia results. Anything interferring with the balance between blood destruction and regeneration will lead to anemia. Early in neonatal life there is a drop because the blood factory is not functioning 100 per cent. As soon as hematopoiesis is well established, there is a rise in red cells and hemoglobin, to approach normal.

Anemias of the Newborn Infant

Robert A. Strong, M.D.,* New Orleans

It has long been realized that a sequence of anatomic and physiologic changes is initiated as soon as the newborn baby begins its independent existence. In so far as the blood is concerned a study of the evolution of neonatal circulation and hematopoiesis indicates that in the blood certain changes take place immediately after the interruption in placental circulation, while others require several weeks or even

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months. The physiologic changes usually proceed in an orderly manner, without any detectable effects on the infant. They are initiated at the time that the antenatal centers of erythrogenic activity cease to function and hematopoiesis is established in the bone marrow. However, when interruptions in this normal sequence occur at or shortly after birth, there follows in the blood of the infant alterations which cease to be physiologic and become pathologic. The consequences of these alterations are referred to as the *anemias of the newborn infant*, and Dr. Abt has requested me to discuss this phase of the subject.

In the complete readjustment which the newborn baby makes to its change in environment, it is most important that an equilibrium between blood destruction and blood formation be established. The surplus of erythrocytes, which are carried over from intrauterine life, is no longer necessary for the maintenance of adequate tissue respiration following the change from the environment of low oxygen tension in utero to a higher oxygen tension after birth. Therefore, a reduction in the number of erythrocytes and a consequent reduction in the hemoglobin which they contain is an important phase of the establishment of normal levels. The reduction in the number of circulating erythrocytes is brought about by hemolysis. This hemolytic dissolution of the erythrocytes releases hemoglobin, which is then taken from the blood stream by phagocytic cells contained within the liver, spleen, and bone marrow, and is split within these cells into bilirubin and a colorless iron-containing residue. The greater part of the bilirubin thus formed passes into the intestines, where it is reduced to urobilinogen, but a small quantity of it is thought to enter the blood stream directly. Most of the urobilinogen is believed to be reabsorbed from the intestinal tract and is returned to the liver through the portal circulation. The hemolytic process, which occurs at birth, causes such a marked overproduction of bilirubin in some instances that the liver is unable to excrete the excessive amount. The bilirubin content of the blood then increases and may be deposited in the tissues, with the result that an icteric tint of the skin appears on the third or fourth day after birth, but gradually subsides within eight to ten days. This, we call *simple icterus neonatorum*. It is rarely accompanied by any detectable effects on the infant and requires no treatment. It apparently is not possible, however, to exclude definitely some sort of functional incapacity of the liver as an additional causative factor of this condition. In support of this belief, its exaggeration and persistence in premature infants have been frequently cited. In these infants, it is reasonable to assume that the liver function is even more decreased than it is in the normal infant.

In addition to simple icterus neonatorum which is fundamentally caused by a reduction of erythrocytes, a certain amount of anemia may be present when the erythrocytes and the hemoglobin descend to the lowest level after birth. This level is reached about the end of the second or third month. It may remain for a short time before the erythrocytes, following the establishment of medullary blood regeneration, begin to increase. Such anemia is spoken of as *physiologic anemia of the newborn infant*. It is likewise inconsequential in its effect on the infant and cannot be influenced by any administration of iron or copper. Simple icterus neonatorum and physiologic anemia of the newborn infant may both be regarded as benign conditions.

In contrast to these two physiologic conditions, certain pathologic states may occur at or shortly after birth, and the resulting anemias provide a fascinating study. I have been interested in them because it has been our fortune, in common with many of you, to see a number of infants presenting variable symptoms. There is much to be learned about these conditions, and consequently I am pleased to have an opportunity to open a discussion of them in order that we all may broaden our knowledge with the observations which some of you may have made.

Many theories have been advanced concerning the etiology of the anemias of the newborn infant, and varying classifications have been suggested. I am going to

resist the temptation further to complicate the situation by refraining from suggesting any other classification. At the same time, I am going to hope that by our exchange of views, we will leave this meeting more enlightened than when we came here. It is difficult to draw a line between the anemias of the newborn infant and what might be spoken of as the anemias of infancy and childhood. I shall, therefore, confine myself to my conception of what should be regarded as the anemias which have their origin at or shortly after birth.

I believe that we are all in accord that most of these anemias occurring in the earliest days of the neonatal period may be grouped under the symptom complex called *erythroblastosis fetalis.* This term has been widely accepted to include icterus gravis neonatorum, hydrops fetalis or universal edema of the fetus, and congenital anemia of the newborn infant. I am aware that there are some variations in these terms, but they are of a minor nature only. It has been difficult at times to separate the three conditions, because clinical, pathologic, and hematologic studies have established many symptoms which they have in common. The first and most important is the presence of considerable numbers of erythroblasts in the blood. These immature red blood cells remain in the peripheral circulation much beyond the time when they should normally disappear. This is referred to as *erythroblastemia.* Moreover, there is evidence of a very active bone marrow and marked extramedullary hematopoiesis, which is chiefly erythropoietic in character. This is referred to as *erythroblastosis.* Jaundice, which is characteristic of icterus gravis, has been found at birth in hydrops fetalis, while edema, which is an outstanding feature of hydrops fetalis, has likewise been noted in icterus gravis, although it is usually localized and of a slight degree. In both, there are splenomegaly and hepatomegaly, a marked anemia, and the characteristic immature red blood cells in the peripheral circulation.

Stransky is of the opinion that there are two rather distinct types of congenital anemia of the newborn infant. One type is characterized by a nonregenerative blood picture and presents but few, if any, features in common with icterus gravis. The other type, however, which is characterized by an embryonal blood picture, is strikingly similar to icterus gravis in that there is often jaundice, hepatomegaly and splenomegaly, erythroblastosis, and erythroblastemia. Diamond, Blackfan, and Baty have clearly shown that in those few instances after the jaundice has disappeared in infants recovering from icterus gravis, the clinical and hematologic characteristics fulfill the diagnostic criteria of what is generally spoken of as congenital anemia of the newborn infant. This, in my opinion, is enough evidence to justify the conclusion that the three closely related clinical disorders—icterus gravis neonatorum, hydrops fetalis, and congenital anemia of the newborn infant—will continue to be grouped under the heading of erythroblastosis fetalis for some time to come.

This assumption is based on the fact that from time to time certain observations have been made which add to the perplexity of their individual indentity, because the similarities in these disorders, based on the clinical, pathologic, and hematologic findings, are subject to wide variations. For example, in each of the three conditions, cases have been reported in which there was little or no evidence of erythroblastosis. The occurrence of both hydrops fetalis and icterus gravis has been noted without the presence of nucleated red blood cells in the peripheral blood. Further, a marked erythroblastemia in icterus gravis has been found even when the red cells have not dropped below 4 million per cubic millimeter. Finally, it is to be remembered, as pointed out by Pasachoff and Wilson, that erythroblastosis is not confined to these conditions alone, as it sometimes occurs in congenital syphilis and sepsis of the newborn infant.

Perhaps the most convincing evidence of etiological relationship is to be found in the familial association of these three conditions. This familial tendency has been observed repeatedly, and it is not uncommon to find in the same family one child born with icterus gravis, another with hydrops fetalis, and still another exhibiting congenital anemia of the newborn. Macklin, Lamont, and Macklin, in tabulating

the incidence of erythroblastosis fetalis in twins, cite a case in which one of the twins was icteric and the other was hydropic. Maharik has recently cited an instance in which one of uniovular twins was affected while the other was normal. It would be most difficult to explain this on a basis other than a common etiology. No single theory has explained adequately the basic hematopoietic disturbances responsible for erythroblastosis fetalis. There are some facts, however, which are quite significant. One is that the majority of these cases which have been reported in otherwise normal families may be nothing other than the onset of a familial occurrence. The plausible explanation was suggested by Josephs a few years ago. The first-born is nearly always spared and less frequently the second-born, but once the disease occurs in a family, subsequent pregnancies almost invariably result in one of the clinical types of erythroblastosis fetalis. Adams and Cochrane have just reported an exception to this in that the third infant in a family, following two affected infants, was normal. They administered liver extract to the mother during her third pregnancy and suggested that this may have been the reason for the unaffected child.

As a rule, a normal pregnancy precedes the birth of an affected infant, but a few observers, particularly Rolleston, have reported the presence of various forms of toxemias of pregnancy. Similarly, with the notable exception of Parsons, who believes that a maternal anemia due to a deficient diet may, at times, cause an anemia in the offspring, most observers have found that anemia and nutritional disturbances did not exist in the mothers. Further evidence that the primary factor does not arise from the mother is to be found in those instances in which a pregnancy resulted in twins, one of whom was affected with erythroblastosis fetalis and the other was normal. Apparently the disease exhibits no racial tendency. Statistical studies, although few in number, offer evidence that icterus is not so common as was once believed. Clifford and Hertig give an incidence of 1 in 340 newborn infants, and Andrew and Miller, 1 in 490.

Sepsis of the Newborn Infant:

Almost any bacteria may cause infection. Those which concern us most frequently are streptococcus, staphylococcus, colon bacillus, and tetanus. The portal of entry to the blood stream is usually the umbilical area, but bacteria may gain entrance through the skin. The symptoms are temperature, jaundice, bleeding, and, of course, some anemia. The blood picture observed in infection in the neonatal period depends upon the severity of the infection as well as the organism. Anemia is more frequent with streptococcus and *B. coli* septicemia than it is with staphylococcus. Infection occurs most often during the latter part of the first week of life and may impede the progress of hematopoiesis during the transition from the antenatal centers of blood production to bone marrow hematopoiesis. Consequently, a fetal type of blood picture with an outpouring of nucleated red cells and immature white cells may characterize the anemia. The newborn infant with congenital syphilis may show this picture, together with jaundice, more marked anemia, enlargement of the liver and spleen, and a tendency to hemorrhage. Winkle's disease should be mentioned at this point, as it is a form of hemolytic anemia which is probably due to infection and is associated with cyanosis, icterus, and hemoglobinuria. There is a widespread tendency at the present time to drop this disease as a clinical entity, because it is apparently indistinguishable from the group of symptoms which follow any sepsis in the newborn infant.

Erythroblastic-Hemolytic Anemia of the Newborn Infant:

There are some anemias which make their appearance in the latter part of the newborn period, when hemolysis is in full progress. Among these are the anemias which accompany congenital acholuric jaundice and what has been spoken of as congenital nutritional anemia. There are still others who believe that erythroblastic

anemia or thalassanemia (Cooley's anemia) may make its initial appearance during this period. It is not an easy task to recognize these anemias in the early stages because they occur at a time of rapidly falling blood levels. Dwyer and Neff consider erythroblastic hemolytic anemias of the newborn infant as being the result of a rapid hemolysis of red cells at this period. They add that it is accompanied by icterus, erythroblastemia, macrocytosis, and a color index of 1.0 or above. They contend that there is often leucocytosis with many immature forms, thrombocytopenia with increased bleeding time, and petechial hemorrhages. They believe that the icterus is not the result of the hemolysis alone, because it is not related to the rapidity in the fall of red cells. Furthermore, they advance the belief that bile "thrombi" plugging the capillaries of the liver cause an obstructive type of jaundice with a prompt, direct, or biphasic van den Bergh reaction.

With the exception of Parsons and his co-workers and Neale and Hawksley, the consensus is that infants born of mothers who have suffered from iron deficiency during pregnancy show a normal blood picture at birth and the influence of inadequate storage does not become manifest until later in the first year. Nutritional anemia or anemia due to iron starvation will be taken up subsequently by Dr. Abt. In the state of confusion which characterizes the blood picture during the latter part of the newborn period, it is difficult for me to understand how a sufficient amount of evidence can be obtained to diagnose an early erythroblastic anemia or thalassanemia. If the infant is of Mediterranean parents, we could suspect the diagnosis, with the idea of proving it later. However, since Foster has reported a definite case of erythroblastic anemia in a Chinese girl, we can no longer consider erythroblastic anemia as being a disease found exclusively in Mediterranean races.

Anemia of Prematurity:

Last year, at a round table discussion on the therapeutics of anemia, Dr. Josephs raised the question as to what is to be considered the anemia of prematurity. I am going to go one step further and suggest that it no longer can be regarded as a clinical entity. I have gained the impression, as doubtless many of you have, that we have too many types of anemia which have so much in common with other types and that the time has arrived when we should at least attempt to reduce the number of designations.

It seems to be very well established that normally a low level of hemoglobin and red cells occurs between the eighth and the twelfth weeks after birth. This is physiologic, and without therapy the hemoglobin and the erythrocyte levels slowly rise during the following four to five months until the normal levels of about 4.5 million red cells per cubic millimeter and 13 to 14 Gm., or 80 per cent or better, of hemoglobin are reached. In the premature baby, hematopoietic activity is generally delayed longer than it is in the full-term baby, so that the resulting anemia is likely to be more severe and to last longer. Josephs suggested this explanation last year and it certainly is plausible. I think that iron is not a factor. A number of years ago, Helen Mackay established the fact that iron administration failed to influence the fall in hemoglobin or erythrocytes and demonstrated that nothing could be done to initiate a rise until normal hematopoiesis is established. We should not be surprised if it is delayed in the premature infant, because every other physiologic function is delayed in this type of infant, who is poorly prepared for independent extrauterine existence. I believe, therefore, that the so-called anemia of prematurity should be regarded as a physiologic anemia of an infant with an impaired anatomic and physiologic development.

DISCUSSION

DR. PHILLIPS.—Does a young infant show at times an ideopathic congenital anemia which does not belong to any of the groups that have been described?

DR. STRONG.—Yes, that would be the third of the group, which I didn't make perfectly clear. Following an icterus gravis, when the icterus clears up, the baby looks very pale underneath the yellow tint. And a mild anemia can follow an infection sepsis of the newborn infant.

CHAIRMAN ABT.—There has been an interesting report in which one man and his wife had several babies born with erythroblastosis fetalis. For some reason or other they separated; after remarriage, normal children were born to the husband's second wife, but the first wife by the second husband gave birth to a baby with erythroblastosis fetalis. The same author reported another family where the same condition occurred, but when husband and wife remarried, abnormal children appeared on the paternal side of the second marriage.

QUESTION.—What about the white blood cell count in erythroblastosis fetalis?

DR. STRONG.—It is not much higher than 20,000; we have had four cases, and that's been about the average figure. The platelets are about 200,000. There is apparently no effect on them.

CHAIRMAN ABT.—In this group of cases are found many nucleated red cells, and the older authors appear to have confused these with white cells. As a result, some of the cases of erythroblastosis fetalis were diagnosed as leucemias.

DR. ANDREWS.—Will Dr. Strong enlarge on his discussion of congenital anemia?

DR. STRONG.—It is one of the group of erythroblastic anemias, less severe than icterus gravis neonatorum or hydrops fetalis. It is due to a delay in the development of the normal postnatal hematopoietic function.

DR. HEARN BRADLEY, NASHVILLE.—Does erythroblastosis underly hydrops fetalis and icterus gravis?

DR. STRONG.—Erythroblastosis fetalis is a symptom complex occurring in congenital anemia of the newborn infant, icterus gravis neonatorum, and hydrops fetalis, all of which are due to the same underlying cause.

DR. BRADLEY.—Does iron help anemia in the first four months of life?

DR. STRONG.—Physiologic anemia of the newborn infant cannot be influenced by any administration of iron or copper. Likewise in those pathologic anemias in which the condition is due to a delay in the development of normal postnatal hematopoiesis, it is unlikely that administration of iron would have any effect until normal hematopoiesis is established. If the "blood factory" is not functioning, no amount of building material will result in increased blood formation.

DR. PIERCE.—It is possible that allergy may be a factor in anemia of the newborn infant.

CHAIRMAN ABT.—The products of blood destruction due to hemolysis in the neonatal period may be stored in the body for subsequent use in the manufacture of new blood when needed.

DR. GARRISON.—Does the condition of the infant's blood bear any relation to that of the mother? Does the mother's diet have any effect on the baby's blood?

DR. WINDLE.—It is doubtful whether there is any correlation between anemia in the mother and in the baby. In rat experiments there is a suggestion of some connection, but there are no facts to prove this correlation in human beings.

DR. T. B. COOLEY, DETROIT.—There is no definite evidence that erythroblastosis fetalis is hereditary, in the sense that it is passed on from one generation to an-

other, although the familial tendency has been repeatedly observed. Anemia of the mother, in my opinion, does influence the development of anemia in the baby.

DR. U. J. BUSIEK, SPRINGFIELD, MO.—The statement was made that the cord should be tied late to allow the infant to obtain more blood. Then it was said that icterus simplex was due to hemolysis of surplus red cells. If surplus cells are being destroyed, why is it advisable to allow the child to obtain even more blood by waiting to clamp the cord?

DR. WINDLE.—Although the surplus cells are not needed at the time they are destroyed, the products of their destruction are, for the most part, stored in the infant's body, and are used later to make new blood cells as need for these arises. Availability of this material for use later in the nursing period is believed to prevent the development of anemia that would otherwise occur if the placental blood were lost by early clamping of the cord.

Anemia of Late Infancy

Arthur F. Abt, M.D., Chicago

I. Hemolytic Disease:

When seen in early infancy, hemolytic disease displays certain differences from the manifestations presented when the first occurrence is noted in later childhood. In early infancy, anemia is often a more pronounced symptom than icterus and is generally quite severe. The onset in the young infant may occur as a severe hemolytic crisis and may terminate fatally. The blood changes are usually exaggerated, both as to size and shape of the red cells. The number of nucleated and reticulated erythrocytes may consist of a very high percentage of the total red cells. Splenomegaly is usually of a considerable degree.

Onset.—The onset, contrary to popular conception, may be noted in the newborn period. I have recently reported a case in which the jaundice was noted at birth. The onset may be insidious, or the condition may develop suddenly and terminate fatally. The earlier in infancy the symptoms appear, the more severe they are likely to be.

Clinical Findings.—The following clinical observations have been noted when the disease occurs in early infancy:

1. Familial Occurrence: The occurrence of this condition in cousins, as mentioned by Parsons, is the only instance in which a familial history is noted when the disease occurs in infancy. Debré has recently reviewed the familial occurrence in fourteen families and believes that the condition is transmitted as a dominant characteristic according to Mendel's law.

2. Jaundice: When the condition is first manifested in early infancy, jaundice may be entirely absent, even though there be indisputable evidence of a considerable increase in blood destruction. The jaundice varies considerably from time to time and is most marked in the remission after the crisis.

3. Anemia: Anemia is always one of the most striking features of the disease in young infants and may be quite severe. In one of my cases, the red cell count fell to 790,000, and the hemoglobin similarly diminished. The color index is usually over 1.

4. Blood Findings: (a) Size and Shape of Erythrocytes: It has been generally believed that one of the diagnostic criteria is the spherocytosis and microcytosis so commonly noted in the condition. Until recently microspherocytosis was indeed a criterion without which the diagnosis could hardly be made. However, it has now been recognized in the older patients suffering from the condition, and particularly in the infants, that neither microcytosis nor spherocytosis is a prerequisite to this condition. Occasionally, as pointed out by Hill, macrospherocytosis may be noted.

The occurrence of macrocytosis surely cannot rule against the diagnosis. The tendency for macrocytosis to be more or less physiologic in the young infant probably accounts for the frequency here noted.

(b) Reticulocytosis: This is a most characteristic finding in this condition. The increase is considerable in young infants. Baty has recorded a case with 92 per cent reticulocytosis in the peripheral blood.

(c) Erythrocyte Fragility: Since the days of Chauffard, increased fragility of the erythrocytes has been one of the outstanding criteria for the diagnosis of this condition. However, the fragility may be normal, or the resistance of the erythrocytes may be even somewhat increased. Debré notes this fact, and E. Schiff has recently reported a typical case with normal fragility of the red blood cells. A normal or even an increased resistance does not rule out the diagnosis.

(d) Other Blood Findings: The white blood count generally ranges from normal to somewhat increased. The number of platelets is usually within normal limits. Occasionally, a considerable rise in the number of platelets have been noted following splenectomy. A certain increase in the number of normoblasts is generally noted. Bilirubinemia is always present. The icterus index is increased, and the indirect van den Bergh test gives a positive reaction.

5. Bone Marrow: Smears of the bone marrow obtained by sternal puncture reveal an increased number of nucleated erythrocytes. Instead of the normal 15 per cent, 50 per cent or over have been noted in this condition. This hyperactivity of the bone marrow is characteristic of hemolytic disease.

6. Splenohepatomegaly: In all cases of this condition the spleen is enlarged. When the disease appears in early infancy, this is particularly true, and the enlargement may extend below the umbilicus and completely fill the left flank. The liver may also show considerable enlargement. Both spleen and liver are firm to the touch.

7. Miscellaneous Physical Findings: Occasionally there may be general glandular enlargement in the older group of patients suffering from hemolytic anemia. This is usually not noted in early infancy.

Cardiac murmurs have been heard. These are probably so-called hemic murmurs due to the anemia.

Difficulties in development and infantilism have been reported, as well as skeletal deformities. However, these are due to the chronicity of the disease, and would not be expected in infants suffering from hemolytic anemia. The association of gallstones with this condition has been reported occasionally.

In older patients ocular lesions may occur, but have been in infancy.

8. Febrile and Hemolytic Crises: The crises which characterize the course of this disease may show different degrees of severity and different manifestations. Generally, the infant manifests prodromal symptoms, such as lassitude, lack of appetite, and fretfulness. This is followed by a deepened jaundice and an increase of anemia. Usually during these periods of crisis the spleen enlarges and the urine becomes dark. Abdominal pain and colic have not been characteristic of the condition in infancy.

Occasionally crises are initiated by febrile attacks and all the symptoms are magnified, and the infant may be extremely prostrated. When fever accompanies the crisis, the anemia is most severe. Periodicity in the occurrence of these hemolytic crises is the rule. The interval between crises varies considerably.

The extent of jaundice and anemia produced by single crises in the same individual will vary considerably from attack to attack.

9. Urine and Stool: The urine contains increased amounts of urobilin, which is especially noted following a crisis. Occasionally hemoglobinuria may be noted. The stools are normal but occasionally of a dark color. Acholia is never present.

Treatment.—The best temporary treatment following a crisis is a transfusion. In an acute crisis, where anemia is so severe that there is danger of anoxemia and

insufficient blood volume, frequent small transfusions must be resorted to, although the transfused blood seems to be much more rapidly hemolyzed when given during the crisis than when given during the interval.

Blood serum has been recommended, and one case here reported, in addition to transfusions during the crisis, also received 200 c.c. of human serum in 20-c.c. doses over a period of several weeks.

The only permanent and successful type of therapy is splenectomy. This operation was inaugurated by Banti in 1903 for this condition. Although the operation carries with it a certain risk, it seems wise to urge that it be performed, even in early infancy. The normal growth and development of the infant following operation, as well as the prevention of certain skeletal and developmental complications which occur during the chronic course of the disease, seem to more than counterbalance the operative risk.

It would seem well to advise the operating surgeon to search for any possible accessory splenic tissue at the time the spleen itself is removed. It has been reported occasionally following splenectomy that improvement resulted for a time and then symptoms returned. Upon second operation, a greatly hypertrophied accessory spleen has been removed. Permanent success, therefore, depends upon the removal not only of the spleen, but also of any accessory splenic tissue.

Following operation, certain changes occur, some of which have already been noted. The crises ceases. Jaundice lessens and usually disappears entirely. Occasionally a subicteric tinge remains, which is especially noted in the sclerae. The anemia rapidly improves, and the blood generally returns to normal. Rarely, following splenectomy, the platelet count rises, sometimes to a marked degree, but usually it subsides to normal range after a period of time. The reticulocyte count gradually drops to normal. Occasionally the microcytosis persists and the fragility of the red cells remains somewhat increased following operation. The increased signs of hemolysis quickly disappear following operation.

Differential Diagnosis.—In the newborn infant, hemolytic anemia must be differentiated from physiologic icterus, anemia of the newborn infant, and erythroblastosis fetalis, sepsis, and congenital syphilis. Congenital obstruction of the bile ducts and congenital hepatic cirrhosis will cause jaundice but not anemia of the hemolytic type. In the neonatal period an early-manifesting case of sickle-cell anemia or Cooley's disease might cause some difficulty in differentiation. When the progress of such an infant is followed and the recurring crises are noted, the differentiation is not too difficult for this condition. The only other condition in which increased fragility of the red blood cells has been noted is toluendiamine poisoning.

In those cases ushered in by an acute hemolytic crisis, one may first be in doubt whether he is dealing with the first attack of hemolytic anemia or whether he is confronted with a type of acute hemolytic anemia described by Lederer. Parsons recently stated that he has observed this latter condition in the neonatal period, although he states that the age incidence is usually above 6 months.

Debré notes that, in his opinion, conditions diagnosed as acute hemolytic anemia of the Lederer type turn out, after careful study, to be hemolytic crises in patients suffering from congenital hemolytic disease. He stressed the fact that final diagnosis of the Lederer type of anemia should be made only if, in the subsequent course, no further attack occurs.

II. Erythroblastic Anemia of Cooley (or Mediterranean Anemia):

This disease has been confined chiefly to infants whose parents have been born in Mediterranean countries. Bywaters, in 1938, reported a case of Cooley's syndrome in an English child, none of whose ancestors came from the Mediterranean countries. It is a familiar disease and may be suspected in the neonatal period when a definite diagnosis has been made in a preceding sibling.

The anemia develops insidiously and is usually not of any considerable degree until the latter half of the first year of life. The characteristic lemon yellow pigmentation of the skin, the mongoloid facies, and the characteristic bone changes revealed by roentgenologic examination do not manifest themselves until the anemia has progressed for some time.

In addition to the gradually developing anemia, the following blood changes are characteristic in a typical case of Cooley's anemia. There is usually a marked erythroblastosis accompanied by polychromatophilia, poikilocytosis, and anisocytosis. While there may be an occasional microcyte present, the macrocytic erythrocytes are the most abundant and typical of the condition. Most of these red cells are characterized by their abnormal thinness. Cooley has pointed out that the most characteristic type of red cell in this condition is a large, pale erythrocyte which is extremely thin and leaflike. He has shown that in wet preparations the edges may fold over and ridges may be formed, and the hemoglobin is distributed in clumps.

In Cooley's type of anemia, the resistance of the red cells to hemolysis is often of a considerable degree. As in hemolytic anemia, sternal puncture reveals an increase far above normal of the number of nucleated erythrocytes.

As the disease develops and the symptoms of anemia progress, the spleen enlarges and may reach great size, as may the liver. The skin assumes a subicteric tint, and occasionally a definite jaundice with yellowing of the sclerae may be manifested. The facies develop a mongoloid appearance which is produced by changes in the skull bones. The changes in the skull also do not appear until some time after the development of the anemia.

In the later stages the roentgenologic changes reflect the extreme marrow hyperplasia. The shafts of the long bones are widened and the cortex is thin. In late cases, the characteristic spicules, appearing as bristly hairs, are noted in a lateral x-ray of the skull. While these x-ray findings are characteristic of Cooley's anemia, it must not be forgotten that they may also be present in other anemias of long duration.

Diagnosis.—The following should be considered in the diagnosis: This is a disease of familial occurrence in infants and children of Mediterranean origin. There is progressive anemia, splenomegaly, Mongoloid facies, yellowing of the skin, and typical roentgenologic changes in the bones.

The blood picture is the chief diagnostic aid. In early cases erythroblastosis may not be as marked as later in the disease. Progressive changes in the blood, which include an increasing erythroblastosis, anisocytosis and poikilocytosis, and the peculiar thinness of the red blood cells, with the unequal distribution of hemoglobin, will confirm the diagnosis in a case which is followed for a long time.

Sickle-cell anemia has been observed in Greek and Italian children and must be differentiated from Mediterranean anemia.

Treatment.—No known treatment is recognized in this country as helpful to erythroblastic anemia. In reports from Greece of cases described as erythroblastic anemia in malaria-infested areas, the authors have been able to demonstrate malarial parasites in the blood; according to their accounts, the disease was cured by intensive antimalarial treatment (quinine, plasmochin, and atebrin).

One can only note that, while malaria may have been the causal factor of these cases reported in Greece, it does not apply to this country, for patients carefully studied in our clinics have never revealed malarial infestation.

III. Congenital Aplastic (Aregenerative) Anemia:

An increasing number of case reports on this apparently rare condition occurring in early infancy gives the impression that possibly the condition has been overlooked and that more cases will be recognized in the future. Apparently, the condi-

tion is of congenital or constitutional origin. The anemia usually manifests itself early in the newborn period and is characterized by its chronicity and the failure of all therapeutic attempts, except frequent blood transfusions, to relieve it.

In 1911, Benjamin described several cases of aregenerative anemia associated with other malformations in young children. He believed the anemia was on a purely functional basis. Finkelstein also noted in 1911 that there is a constitutional type of anemia in the newborn period. Stransky (1925) reported several cases of aregenerative anemia in early infancy. Hugh Josephs, in 1936, reported the cases of two infants suffering with a constitutional type of anemia. He noted an aplastic anemia which was apparently due to a failure of erythropoiesis which was so marked that the patient could be kept alive only by transfusions.

Recent interest in this condition was stimulated by the report of Diamond and Blackfan, who used the term "hypoplastic anemia" to describe the disease. They reported four cases of this type of anemia, beginning early in infancy, with no hemorrhagic tendency, moderate leucopenia, and the production of a small and inadequate number of reticulocytes from the bone marrow. The bone marrow smears revealed a reduction in the number of nucleated red cells, as recently shown in the case reported by Margrit Esser. Apparently, the aplasia is confined to erythropoiesis; the other cellular elements seen to be normal.

According to Diamond and Blackfan, two theories as to the etiology of this condition may be considered. One is that there may be a congenital insufficiency of the red bone marrow which fails to produce mature erythrocytes when needed; life can be sustained only by repeated transfusions of mature erythrocytes. The second theory has to do with an error in the metabolism of some blood building substances, which results in a deficiency state.

As has been noted, every form of therapy, with the exception of transfusion, has failed in the cases reported. No therapy stimulates hematopoiesis, and these infants are kept alive by substitute transfusions. Growth and development may proceed fairly normally in such an infant, if the transfusions are repeated. Some of these infants have made astonishingly good progress, even when fairly low levels of red cells and hemoglobin values were maintained, and these patients apparently adjust themselves to these lower levels without showing diminution in activity or in appetite, or other symptoms of anoxemia. I have seen one such case through the courtesy of Dr. Irwin Rubell of Chicago, and this child (as in one of the cases reported by Diamond) is now able to regenerate sufficient erythrocytes and hemoglobin to go without transfusions. The ultimate prognosis in this condition is extremely uncertain, and the only treatment is repeated transfusion.

IV. Letterer-Siwe's Disease:

This condition, occurring in early life, is characterized by anemia, generalized lymphadenopathy, splenohepatomegaly, hemorrhagic cutaneous manifestations, and osseous changes. The pathologic picture is characterized by widespread hyperplasia of the macrophages, without lipoid storage in the various organs. The condition is neither hereditary nor familial. All reported cases have occurred in infants or young children. The disease is of unknown etiology, with fatal prognosis, and duration varies from a few weeks to several years. It is a disease which involves the reticuloendothelial system and may be termed a reticuloendotheliosis.

Each author who attempts an analysis of this intriguing condition gives it a new name. E. Glanzmann, in April, 1940, reported the condition under the title of "Infectious Reticuloendotheliosis (Abt-Letterer-Siwe's Disease) and Its Relation to Schüller-Christian Disease." In September, 1940, Arvid Wallgren reported it as "Systemic Reticuloendothelial Granuloma (Nonlipoid Reticuloendotheliosis) and Schüller-Christian Disease."

The anemia is of a progressive, secondary type and usually manifests itself with a white blood cell count varying from a moderate leucocytosis to definite leucopenia.

The localized skeletal changes, as well as the cutaneous manifestations, have been shown pathologically to be due to proliferation of reticuloendothelial cells in the affected areas.

Wallgren's recent review seems to agree with our conclusions that infection does not play a causative role in this condition. The younger the patient at the onset of the condition, the more malignant the course will probably be. Both Glanzmann and Wallgren feel that Letterer-Siwe's disease and Schüller-Christian disease are different types of the same malady. The malignant type of the disease, with the short course, appearing in infants, is a nonlipoid reticuloendothelial hyperplasia. According to these authors, when the condition occurs in adults and older children, it runs a more protracted course; reticulum cells have time to ingest large amounts of cholesterol, and the foam cells typical of this type of the disease (Schüller-Christian type) predominate. In the malignant type occurring in infancy, where the anemia is rather severe and the disease is rapidly fatal, there is no treatment.

V. Anemia Accompanying Infection:

The anemias that are caused by and accompany the acute infections, especially the upper respiratory diseases, are probably the most common encountered in young infants. The anemia due to infection is not an entity, however, but merely a symptom, and will vary according to the direct or indirect effect the infection may have on the blood-forming organs. The infection may cause a diminished production of erythrocytes by a so-called toxic suppression of the bone marrow, or a diminution of erythrocytes by increased hemolysis, which would be termed a hemolytic anemia. There may, of course, be a combination of both mechanisms in any given case.

The anemia in these mild infections is usually of a slight and secondary nature, and will yield quickly as soon as the infection is cleared up. However, a succession of colds or upper respiratory infections may produce a more severe anemia; the anemia in turn aggravates the infection through lowered resistance of the infant, rendering him more susceptible and the infection more difficult to clear up. Thus, the more infection, the more anemia, and the more anemia, the more susceptible the infant is to infection.

It should be noted in this connection that as long as the active infection is in progress, it is extremely difficult to affect the anemia permanently by any form of therapy. It is only after the baby is afebrile and on the way to recovery from his infection that therapy will be at all effective.

VI. Anemias of Nutritional Deficiency:

The anemias of purely alimentary or nutritional origin have been long considered in etiological discussions as having an important place in the classifications of the anemias of infants.

We may recall that following the early hemolysis of red blood cells in the newborn period, a certain supply of available iron is present to meet the demands of rapidly increasing blood volume which corresponds to the general rapid growth in the infant in the first half year. We then realize that the building stones for new blood formation may be used up if new materials are not furnished in the diet. Two facts should be here noted. Mackay has observed that those infants with lower birth weights tend to have lower hemoglobin values as they develop. In other words, the baby with the lower birth weight is growing more rapidly and will therefore exhibit a greater demand for new blood formation than the heavier, more slowly growing infant.

Further, milk, both human and cow's, is low in iron content. As cow's milk contains less iron, it follows that artificially-fed infants tended to show lower hemoglobin curves than wholly breast-fed infants. Krasnogorski, in metabolism experiments, showed that the iron retention of infants on human milk was greater

than that of infants on cow's or goat's milk. It was formerly held that goat's milk anemia was caused by the same essential etiological factors as cow's milk anemia. Recently it was thought that a deficiency of the "extrinsic factor" present in liver and yeast might be responsible for the production of goat's milk anemia. This factor is a component of the vitamin B complex. While goat's milk is not entirely lacking in this "extrinsic factor," the fact that this anemia can be cured by liver and not by iron points to a deficiency of this component of the vitamin B complex as the causative factor in producing goat's milk anemia.

There is good evidence to believe that alimentary or nutritional anemia is caused by a simple insufficiency or lack of blood-building material, especially iron, in the diet. The older theories proposed, such as hereditary predisposition, injurious products in cow's milk (fat injury of Czerny), lack of fresh air and sunlight, and functional weakness of blood-forming organs, need no longer be considered.

Just as other imbalances in infant nutrition may produce disturbances, it can be said that alimentary anemia is not directly due to an injurious effect of cow's milk or any of its constituents. The same anemia may develop in an exclusively breast-fed infant.

The whole nature of the process depends on the proper supply of the necessary blood-building materials, which the infant on an exclusive, long-continued milk diet lacks. The error is not one of commission, but rather one of omission. It is not what we are giving the infant, but what we are failing to give him, that is causing the anemia.

The early addition to and the balancing of infant diets, which is becoming more and more of common usage and knowledge, is greatly reducing the incidence of pure alimentary anemia.

VII. Anemia of Scurvy:

In reports of adults suffering with scurvy, anemia is a common complication, and the vitamin C deficiency is supposedly responsible for this anemia. However, in reports of scurvy in the infant, anemia is not constantly associated with scurvy. According to Hans Aron, it is often difficult to determine whether one is dealing with a scurvy accompanied by an anemia or with an alimentary anemia complicated by scurvy. In recent experiments with guinea pigs, Aron was able to show that anemia did not develop in young guinea pigs weighing approximately 250 Gm., on a scorbutic diet. On the other hand, when adult pigs weighing approximately 400 Gm. were made scorbutic, anemia regularly developed. We may conclude, therefore, that when anemia accompanies infantile scurvy, the anemia is not due to a deficiency of vitamin C per se, but that other elements as iron and protein are probably also lacking in the infant's diet. In adult scurvy, however, a lack of vitamin C probably has some direct connection with the production of the accompanying anemia.

VIII. Anemia Due to Drugs:

A severe aplastic anemia may accompany the administration of certain drugs such as arsphenamine, nirvanol and other coal-tar products, and sulfanilamide. Poisoning with lead and benzol may cause severe aplastic anemia. Exposure to x-ray and radium may also produce an aplastic anemia.

These anemias due to drug poisoning may clear up rapidly if the drug is withdrawn. On the other hand, the anemia may persist with great stubbornness if serious damage has been done to the bone marrow. The blood changes following administration of sulfanilamide and related compounds are of special interest at present. A slight rise in the reticulocyte count level has been reported following the administration of sulfanilamide. Severe hemolytic anemia may follow administration of even small doses of sulfanilamide. Leucopenia may develop, and agranulocytosis and granulocytopenia have also been reported.

It should be emphasized that frequent blood counts should accompany the administration of these drugs, and the drug should be immediately discontinued when unfavorable response of the bone marrow is noted from the blood count.

One should also remember that if a patient has once had a leucopenia with an acute hemolytic anemia or a purpura hemorrhagica in the course of therapy with sulfanilamide or its derivatives, it is quite likely that, if the drug is administered a second time, the patient may have another earlier and probably more severe toxic reaction. Patients who have had a toxic reaction with one of the sulfanilamide derivatives may have a similar reaction with another member of the group. A careful history as to previous toxic manifestations due to sulfanilamide and its derivatives should always be elicited before the drug is started, and care should be used when changing from one derivative to another if toxic manifestations have followed the use of one derivative of the sulfanilamide group.

Time does not permit a separate discussion of the specific anemias associated with malaria, hookworm, and *Bothriocephalus latus* infections, and those accompanying rheumatic fever, syphilis, and other infections and diseases.

DISCUSSION

DR. COOLEY.—In certain families there is a hemolytic constitution. This occurs as a dominant characteristic, and if either parent has it, the children will. In recent years Cooley's disease has been found not to be confined to the Mediterranean races, although formerly it had been so reported.

DR. H. W. DARGEON, NEW YORK CITY.—Is there any evidence that a deficiency in vitamins other than the "extrinsic factor" might be a cause of goat's milk anemia?

CHAIRMAN ABT.—There might be a vitamin B deficiency.

DR. BRADLEY.—How important is it when giving sulfanilamide and allied drugs to check up on the infant's blood for evidence of anemia?

CHAIRMAN ABT.—One should be on the lookout for clinical signs of anemia, and the blood should be examined if the drug is given over any length of time.

DR. COOLEY.—Results with sulfanilamide should be obtained rather quickly if at all, so the drug should not be continued too long if no benefit is noted.

Academy News

Dr. Henry L. K. Shaw, of Albany, N. Y., died March 26 of heart disease, after a brief illness. Dr. Shaw initiated and organized the division of child hygiene of the New York State Department of Health, the first state department of its kind. He has been interested in all pediatric organizations in this country, particularly the American Child Hygiene Association. He was president of the American Pediatric Society in 1929, at its St. Louis meeting.

Region II of the Academy will meet at the Hotel John Marshall, Richmond, Va., on April 24 and 25, 1941. There will be round table discussions on Mental Health of the Child, Nutrition of the Child, and Communicable Diseases and Their Relation to the Child, all as related to national defense.

Region IV of the Academy will meet at the Fairmont Hotel, San Francisco, on May 1-3, 1941. There will be four scientific sessions consisting of papers, case reports, and panel discussions during the mornings and afternoons of May 2 and 3. In addition, two other features have been added to the program: first, a pre-session

day (Thursday) devoted to clinics at the University of California Hospital under Dr. F. S. Smyth and at Stanford Hospital under Dr. H. K. Faber; second, a scientific exhibit arranged to portray recent developments and unusual or rare cases of interest to pediatrics.

The Annual Meeting of Region III of the Academy will be held in Chicago at the Palmer House, May 15, 16, and 17, 1941. There will be a scientific program, numerous regional committee meetings, entertainment, and exhibits. Fellows of the Academy are urged to attend, and all physicians interested in pediatrics who are not Fellows are cordially invited to attend all the activities of the meeting. Hotel reservations should be secured in advance, directly from the management.

On Thursday morning, May 15, there will be a symposium on the Newborn Period, and Thursday afternoon, a symposium on Practical Clinical Topics. Luncheon on this day will be a testimonial occasion in honor of Dr. Abt, Dr. Brennemann, and Dr. Cooley, "the ABC's of Pediatrics." On Friday morning, May 16, there will be a symposium on Neurologic Examination and Conditions in Children, and Friday afternoon, a panel discussion on Growth and Development. The final session on Saturday morning, May 17, will be symposium on Problems of the Adolescent Child.

News and Notes

In April, a series of six lectures on infantile paralysis by outstanding medical authorities will be presented at Vanderbilt University, Nashville, Tenn. These lectures are sponsored by the **National Foundation for Infantile Paralysis.**

Dr. Ernest W. Goodpasture, head of the Department of Pathology at Vanderbilt, is supervising the arrangements. Eminent authorities from all parts of the country will be brought to the University to give the lectures which have been designed to cover thoroughly the entire field of the disease.

The schedule is as follows:

Monday, April 7	The History of Poliomyelitis (Progress of knowledge of the disease up to the present)	Dr. Paul F. Clark, Professor of Bacteriology, University of Wisconsin School of Medicine
Tuesday, April 8	The Etiology of Poliomyelitis (Including its relation to diagnosis)	Dr. Charles Armstrong, Senior Surgeon, United States Public Health Service
Wednesday, April 9	Immunity to Poliomyelitis (Including serum, therapy, and vaccination)	Dr. Thomas M. Rivers, Director, Hospital of the Rockefeller Institute for Medical Research
Monday, April 14	Pathology and Pathogenesis of Poliomyelitis	Dr. Ernest W. Goodpasture, Professor of Pathology, Vanderbilt University School of Medicine
Tuesday, April 15	Epidemiology of Poliomyelitis	Dr. John R. Paul, Yale University School of Medicine
Wednesday, April 16	Treatment and Rehabilitation of Poliomyelitis Patients	Dr. Frank Ober, Assistant Dean, Harvard University Medical School

The lectures will be so designed and prepared that they will serve as material for a publication by the National Foundation, intended to constitute a recent survey of the field of infantile paralysis.

Comments

Pediatrician? Pediatrist?

From time to time the question has been raised as to the policy of the JOURNAL on the use of these words. In the past, either has been allowed, according to the desire of the author, provided the use was consistent. Twice the JOURNAL has published addresses using both words in the same article. Both instances were Academy presidential addresses, as it has been the attitude of the Editors that a "Presidential Address" should not be edited except for obvious grammatical errors or spelling. *Pediatrician* has been and is the word in common usage, although it is well known that it is of mixed derivation from Greek and Latin roots. To the best of our recollection, we first heard the late Dr. Holt use the word *pediatrist,* although much more vivid in the memory of many is an armchair diatribe on the subject of the two words by John Ruhräh, and the seathing way in which he would refer to *pediatrician* as "that bastard word." From the standpoint of editorial policy, both words have been allowed, with the thought that while *pediatrist* was a more correct word than *pediatrician,* the latter had the validity of usage.

Recently a letter was received by the Editors which, while rather startling, has a most amusing side, and we cannot help but gently chide the "purists" who have insisted on calling themselves "pediatrists." Dr. Caulfield, our Academy Historian, became, as he writes, "bothered about the indiscriminate use of pediatrician and pediatrist"; and so he wrote to his friend, the eminent classicist, Dr. George L. Hendrickson, Emeritus Professor of Greek and Latin at Yale. Dr. Caulfield sent us Dr. Hendrickson's reply, from which we quote:

> "*Pediatric*(s) is apparently of modern manufacture, and no such composite as *παιδ-ἰατρικός* occurs in Greek, though I believe it could have been made in that form if they had had occasion to use the word. To the adjective *ἰατρικός* has been added in the English word the Latin suffix *-ian,* just as Greek *φυσικός* becomes *physician.* The same procedure and analogy can only yield *pediatrician,* the title to which is none too flawless and clear however.
>
> "*Pediatrist* has still less claim. In order to be acceptable the word for heal, that is the verb, must have been *ἰατρίζειν,* which does not occur, like sophist (*σοφίστης*) from *σοφίζειν.*
>
> "Etymologically, therefore, *pediatrician* is preferable to *pediatrist,* though not without a blot on its own 'scutcheon. If one

> wished a shorter word than *pediatrician*, the form *pediater* might follow the example of *psychiater*, which the Diet. gives, though not in use I imagine . . . if usage is at all equal I should choose *pediatrician*."

As this information regarding *pediatrist* was in conflict with the ideas we had somehow acquired in the past, we referred the subject to two other classicists. One, headmaster of a boys' school, agreed completely with Dr. Hendrickson. The other, a former professor of Greek and now president of one of the larger midwestern universities, writes:

> "The comments by Professor Hendrickson are entirely correct. I would however put it this way: 'Pediatrist' is the better Greek formation and would etymologically be preferable; 'Pediatrician' is, however, in my opinion more established in usage, and though a hybrid, is well warranted by analogy with many other instances in word formation. . . . I should vote for it."

There the matter rests. While it has been common knowledge that *pediatrician* is an "illegitimate" word etymologically, being derived from the Greek roots of "child" and "to heal" or "to treat" combined with a Latin suffix, we now find that a part of *pediatrist* comes from a nonexistent Greek word! *Pediatrician* is as legitimate as *pediatrist* or physician. To those who must be "pure," we suggest calling themselves "physicer," and "pediater." As far as the JOURNAL is concerned, it refuses to take sides in the quarrel and show favoritism between these two illegitimate children. The Editors give fair warning, however, that if any future president of the Academy feels called upon to use the word *pediater* in his annual address, the Editors will take the privilege of editing it to *pediatrician*.